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101 Cases in Neonatology

Index of suspicion in the nursery

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Index of Suspicion in the Nursery

1 A Blueberry Muffin Rash Complicated by Cardiomyopathy

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PRESENTATION

A 2.4-kg male infant is born at 35 weeks and 3 days of gestation via cesarean section to a 26-year-old gravida 3, para 1 woman whose pregnancy is complicated by dichorionic, diamniotic twins, preterm labor, and decreased variability of fetal heart rate. Maternal serologic findings are normal, other than a nonimmune rubella status. Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. He is transferred to the NICU because of hypoglycemia, which is corrected with dextrose infusion. His female twin sibling has an uneventful newborn course.

Initial examination is unremarkable except for multiple scattered, nonblanching, purple nodules, and macules (Figs 1 and 2), each measuring approximately 5 mm, found on the face, torso, arms, and legs with sparing of the palms and soles and hepatosplenomegaly.

LABORATORY STUDIES

Rubella titers (IgG 16.5 IU/mL, IgM <20 IU/mL) suggest passive maternal immunity and no evidence of current infection. Urine cytomegalovirus is negative. A complete blood cell count demonstrates leukocytosis of 45,000/ μ L (45×10^9 /L) with 12% blasts, 11% polymorphonuclear neutrophils, 14% lymphocytes, and 48% monocytes. Complete blood cell count at 24 hours confirms a white blood cell count of 88,000/ μ L (88×10^9 /L) with similar differential.

DISCUSSION

Differential Diagnosis

These results focused the differential diagnosis on hematologic causes, including congenital acute myeloid leukemia (AML), juvenile myelomonocytic leukemia, and transient myeloproliferative disorder. Bone marrow biopsy revealed a marked increase in monocytic cells, with atypical and immature forms, and 51% blasts. Flow cytometry showed an abnormal blast population with expression of myelomonocytic antigens with aberrant features, including loss of CD13 and CD14, and CD56 expression.

Actual Diagnosis

The infant was diagnosed as having congenital AML with monocytic differentiation.

Patient Course

Induction chemotherapy was administered using the protocol of the Children's Oncology Group AAML1031, which includes a low cumulative dose of

AUTHOR DISCLOSURE Drs Schiff, Supples, Walsh, Russell, and Pylipow have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Characteristic blueberry muffin rash on lower extremity.

daunorubicin (67.97 mg/m^2). Bone marrow biopsy after induction showed minimal residual disease, a favorable prognostic sign. Prolonged marrow suppression, however, precluded further chemotherapy. The infant's course Lucrezia was complicated by respiratory failure, subglottic stenosis requiring tracheostomy, and anthracycline-induced cardiotoxicity.

Pretreatment echocardiography demonstrated a structurally and functionally normal heart. By 2.5 months of age, he developed an increasing oxygen requirement and pulmonary edema. Echocardiography revealed moderately depressed left ventricular (LV) function (shortening fraction [SF] 20%) and LV dilation. His B-type natriuretic peptide (BNP) reached 950 pg/mL (950 ng/L ; normal $<100 \text{ pg/mL}$ [100 ng/L]).

The infant's heart failure was initially managed with furosemide and milrinone. At 4 months, he made a transition to an oral regimen of enalapril, furosemide, and spironolactone with stable echocardiographic findings of



Figure 2. Characteristic blueberry muffin rash on torso.

moderate to severely depressed LV function (ejection fraction [EF] 30%, SF 15%).

At 1 year, a mild recovery of function was seen (EF 47%, SF 23%, BNP of 75 pg/mL [75 ng/L]), but by 13 months of age he developed overt heart failure in the setting of a viral illness (BNP of $4,889 \text{ pg/mL}$ [$4,889 \text{ ng/L}$], and Lucrezia alanine aminotransferase of $2,067 \text{ IU/L}$ [$34.5 \text{ } \mu\text{kat/L}$] with moderate to severely depressed biventricular function. He was evaluated as a candidate for heart transplantation. Because of worsening heart failure, he was placed on a biventricular assist device at 22 months of age. Despite aggressive cardiac support, he developed worsening pulmonary edema and renal failure requiring venoarterial extracorporeal membrane oxygenation (ECMO). He went on to develop multiorgan failure and ECMO was withdrawn. Remarkably, even up until his death at 23 months of age, his AML was in remission, despite having received an incomplete course of chemotherapy.

The Condition

Leukemia is the most common pediatric cancer, with AML representing 20% of cases. (1) Current AML treatments achieve 60% to 70% survival but relapse rates approach 50% (2) and survivors often experience treatment-related morbidity, particularly cardiotoxicity. (1) Congenital leukemia is rare ($<1\%$ of childhood leukemias) but has the highest mortality rate of all neonatal malignancies. AML represents half to two-thirds of congenital leukemias. (2) The most common subtypes are monocytic, myelomonocytic, and megakaryocytic.

Congenital leukemia is defined by presentation in the first 4 weeks after birth; proliferation of immature myeloid, lymphoid, or erythroid cells, with infiltration into extra hematopoietic tissues; and the absence of another diagnosis producing a leukemoid reaction. (3) AML is more common in male infants (2:1) (3) and typically presents with hepatosplenomegaly and infiltration into skin known as leukemia cutis or "blueberry muffin" rash. Lesions are palpable red, purple, or blue cutaneous nodules or macules containing leukemic cells. Central nervous system involvement is less common than with acute lymphocytic leukemia (ALL). Leukostasis and bleeding from thrombocytopenia lead to central nervous system and pulmonary complications. (2)

Congenital leukemia is cytogenetically distinct from leukemia in older children. Neonatal cases possess a rearrangement of the mixed-lineage leukemia (*MLL*) gene located at chromosome 11q23. *MLL* gene rearrangements are observed in 80% of ALL cases and 60% of AML cases diagnosed in the first year after birth. (3) It is believed that most cases of neonatal and infant leukemia arise in utero, sometimes causing fetal hydrops. Risk factors have not been delineated. (3)

Although congenital ALL has a poor prognosis, AML survival in infants nears that of older children. (2) Treatment regimens for AML have a backbone of cytarabine and anthracyclines, with stem cell transplantation for those with high-risk features. (1) Unfortunately, there is significant risk for anthracycline-induced cardiomyopathy, which correlates closely with the cumulative dose. (3) The current patient developed cardiotoxicity despite a low cumulative dose of daunorubicin, perhaps because of risk factors such as young age (<4 years old) and low weight. Cardiotoxicity develops from the accumulation of toxic anthracycline metabolites, and the production of reactive oxygen species. Three forms of cardiotoxicity are described, including immediate pericarditis/myocarditis, early-onset progressive congenital heart failure, and late-onset cardiotoxicity developing years later.

Genetic factors are being identified. (4) Patients with the GG allele on the *CELF4* gene have a 10-fold increased risk of cardiomyopathy over patients with GA or AA genotypes. (5) Carbonyl reductase (CBR) polymorphisms modify the dose-dependent risk. Patients with the CBR3 GG allele, have increased risk despite low- to moderate-dose anthracyclines. (4) Testing for these alleles is not yet commercially available. In transgenic mice, upregulating the carboxyl terminus of heat shock protein 70-interacting protein (CHIP) offers some protection. (6) As genetic testing becomes available, high-risk patients may be identified and receive tailored therapy.

Dexrazoxane, a free radical scavenger, attenuates anthracycline-induced cardiotoxicity, but concerns remain that it may also protect tumor cells from chemotherapy. One randomized control trial suggests that cardiac injury is reduced without compromising antileukemic efficacy (6) and another retrospective cohort study showed no increased risk of relapse. (7)

Trials addressing the management of anthracycline-induced cardiomyopathy in children are lacking. Angiotensin-converting enzyme (ACE) inhibitors, because of afterload reduction, can protect against hypertrophic remodeling. Treatment of symptomatic heart failure includes diuretics, digoxin, and afterload-reducing agents, such as angiotensin-receptor blockers and ACE inhibitors. Mechanical circulatory support serves as a bridge to cardiac transplantation. (8)

Lessons for the Clinician

- Although rare, AML has higher mortality than neuroblastoma, the most common neonatal malignancy.

- Presentation of congenital AML (up to 4 weeks of age) typically presents with hepatosplenomegaly and/or leukemia cutis caused by leukemic infiltration.
- Anthracycline-induced cardiomyopathy is a common complication of chemotherapy for AML.

American Board of Pediatrics, Neonatal-Perinatal Content Specification

- Know the clinical and laboratory features of congenital leukemia

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Index of Suspicion in the Nursery

2 A Large Prenatally Undiagnosed Mass in a Preterm Infant, What Could It Be?

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AUTHOR DISCLOSURE Drs Ibrahim, Pavageau, Miller, Timmons, Wickiser, Piper, Dariya, and Brion have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2.2-kg female infant is born at 28 4/7 weeks' gestation to a 21-year-old gravida 1, para 0 woman with adequate prenatal care. During pregnancy, the mother is treated for *Chlamydia* with repeat negative cultures. She has negative serologies and a normal fetal ultrasonographic scan at 20 weeks' gestation. Delivery is via cesarean section due to premature labor and frank breech presentation. At delivery, the infant is noted to have no respiratory effort and a large sacrococcygeal mass (Fig 1). Positive pressure ventilation is started and the infant undergoes intubation 3 minutes after birth.

The admission physical examination findings are significant for a sacrococcygeal nodular, firm and nonpulsatile 20×30-cm mass, with minimal ulceration that is displacing the lower limbs anteriorly. Magnetic resonance imaging (MRI) of the pelvis shows a presacral mass with a large external component and relatively small internal component; the cephalad portion of the mass occurs at the level of L5, splaying the aortic bifurcation (Fig 2). The infant's vital signs are stable with minimal ventilatory support. Laboratory studies are positive for anemia (hemoglobin 11.4 g/dL [114 g/L]), a normal α -fetoprotein (AFP) level for gestational age (60,500 ng/mL [60,500 μ g/L]), and a slightly elevated aspartate aminotransferase level (141 IU/L [2.35 μ kat/L]).

On day 2 after birth, the infant develops hypotension and worsening respiratory failure; she is started on inotropes and high-frequency oscillation. The lesion becomes more tense and darker in color, concerning for intrasacral hemorrhage. The infant also develops thrombocytopenia (platelets 66,000/ μ L [60×10⁹/L]) and receives multiple platelet and red blood cell transfusions in preparation for surgery. Resection of the mass takes place at the bedside because of the infant's hemodynamic instability and inability to be safely transported with the oscillator to the operating room. The 8-hour procedure is conducted in 2 stages. The initial abdominal approach allows for ligation of the 2 small feeding vessels emerging from the internal iliacs. The infant is then placed in a prone position, for the subsequent sacral approach to resect the mass including the coccyx (Fig 3). The infant has an estimated blood loss of 400 mL, and receives large-volume

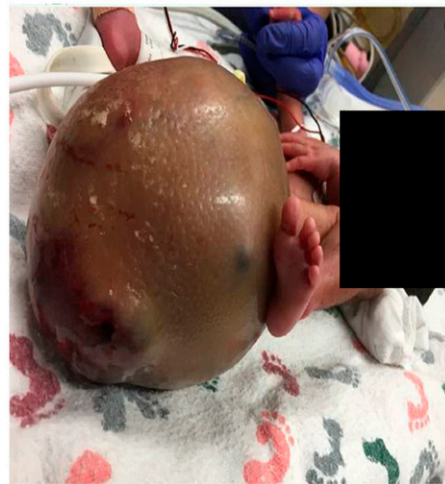


Figure 1. Infant at delivery noted to have large sacroccoccygeal teratoma.

fluid resuscitation (~ 240 mL/kg) and inotropic and vasopressor support. Inotropic support and high-frequency ventilation are discontinued within 24 hours. She is started on enteral feeds 1 week after surgery and is discharged from the hospital at 38 weeks' postmenstrual age. Macroscopically, the resection specimen is a 715-g predominantly solid mass with cystic areas, and measures $14 \times 13.5 \times 11.7$ cm. Microscopic examination reveals a mixture of tissues representing all 3 embryonic layers, including brain and squamous epithelium (ectoderm); ciliated respiratory type epithelium; mucous glands with goblet cells and liver (endoderm); and kidney, smooth muscle, and cartilage (mesoderm), along with immature neuroectodermal epithelial elements, which defined the teratoma as immature (Fig 4). AFP levels were followed, reaching their highest value 1 month after birth ($416,195$ ng/mL [$416,195$ μ g/L]) followed by a steady decline.

DISCUSSION

The Condition

Teratoma is a Greek word that translates into "monster tumor."⁽¹⁾ (2) Teratomas are the most common germ cell tumors of the fetus and neonate. The term *teratoma* was first applied by Virchow in 1869 to a tumor originating from the sacroccoccygeal area. Sacroccoccygeal teratoma (SCT), the most common congenital tumor, accounts for about 35% to 60% of all teratomas and occurs in 1 in 35,000 to 40,000 live births. It is more prevalent in female fetuses, occurring at a female-to-male ratio of 4:1.

Teratomas can be solid or cystic, benign or malignant. They are usually composed of germ cell tissues including the 3 embryonic layers (endoderm, mesoderm, and ectoderm). Teratomas can occur anywhere in the body

particularly along the midline. In neonates, teratomas are most often located within the sacral area.

Three theories for the origin of teratomas have been proposed. (1) The first theory postulates that teratomas originate from the endodermal cells of the yolk sac near the origin of the allantois (totipotent primordial germ cells). During the 4th and 5th week of embryonic development, these cells migrate to the gonadal ridges but if they miss their migration target, they may give rise to a teratoma anywhere from the brain to the coccygeal area. Another theory proposes that teratomas develop from the remnants of the primitive node. During the 3rd week, midline cells at the caudal end of the embryo give rise to all 3 germ layers

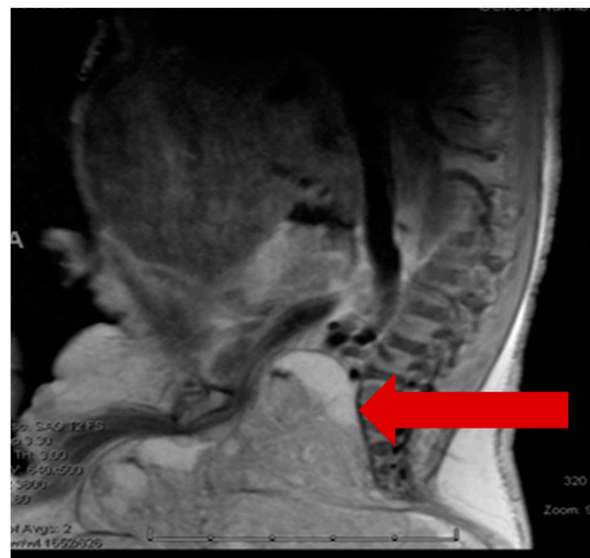


Figure 2. Magnetic resonance imaging scan of the pelvis showed a presacral mass (red arrow) with a large external component and relatively small internal component.



Figure 3. Photograph of the neonate with a sacrococcygeal teratoma mass before (A) and after (B) resection.

and the remaining primitive streak shortens and disappears. The last theory describes teratomas as incomplete twinning.

SCTs can be part of the Currarino triad (anorectal malformation, sacral anomaly, presacral mass). Rare syndromes associated with teratomas are Klinefelter syndrome (strongly associated with mediastinal teratoma), trisomy 13, trisomy 21, and Beckwith-Wiedemann syndrome as well as Proteus and Schinzel-Giedion syndromes. Teratomas in most of the cases are isolated in presentation.

Teratomas can be gonadal or extragonadal. In 1974, Altman et al classified SCTs into 4 types based on location (3): Type I: The most common type is predominantly external with a minimal presacral component.

Type II: Tumors are external with a significant intrapelvic component.

Type III: Tumors are external but with significant pelvic and intraabdominal extension

Type IV: Entirely presacral tumors, with no external components.

Histologically, teratomas are classified as mature or immature based on the presence of the immature neuroectodermal components. However, grading of immature teratomas is of little importance in neonates, as the management and prognosis are not altered. A solid tumor has components of skin elements, neural tissue, fat, muscle, and cartilage as well as hair or bone. Rare parts such as respiratory epithelium, fingers, teeth, rudimentary heart, or a complete eye have been described.

Although the majority of SCTs are benign, 11% to 35% will contain malignant elements. Malignancy risk increases with

age, in males, and with incomplete resection. The most common malignant component is an AFP-producing yolk sac tumor. Histologic detection of small foci of yolk sac tumor may be difficult in very large tumors, and AFP levels may be difficult to interpret because of the wide range of normal values in infants. A mature teratoma may reoccur months or even years after resection as a malignant yolk sac tumor (10%).

In utero, SCTs can cause maternal proteinuria, hypertension, or edema, symptoms similar to preeclampsia. “Maternal mirror syndrome” or “Ballantyne syndrome” has been reported in some cases. Prenatal SCTs may go unnoticed until late in gestation. However, an elevation in maternal serum AFP from an incompletely skin-covered mass could be an indication.

Polyhydramnios associated with fetal hydrops or placental edema can develop because of fetal anemia secondary to SCT tumor hemorrhage. Less commonly, oligohydramnios from obstruction of the fetal urinary tract has been reported. SCTs, particularly solid tumors, can be highly vascular, and a fetus can develop high cardiac output failure, anemia, and ultimately hydrops.

The 2-dimensional ultrasonography performed during pregnancy has resulted in a high rate of SCT detection. The detection of solid components within a tumor is critical because it is associated with a high risk of malignancy and fetal hydrops due to high cardiac output. Once a sacral mass is identified, an evaluation of the distal spine and brain is warranted to rule out meningomyelocele. MRI is superior to ultrasonography, with regard to contrast resolution, improved tumor demarcation, and vascular perfusion of a mass, as well

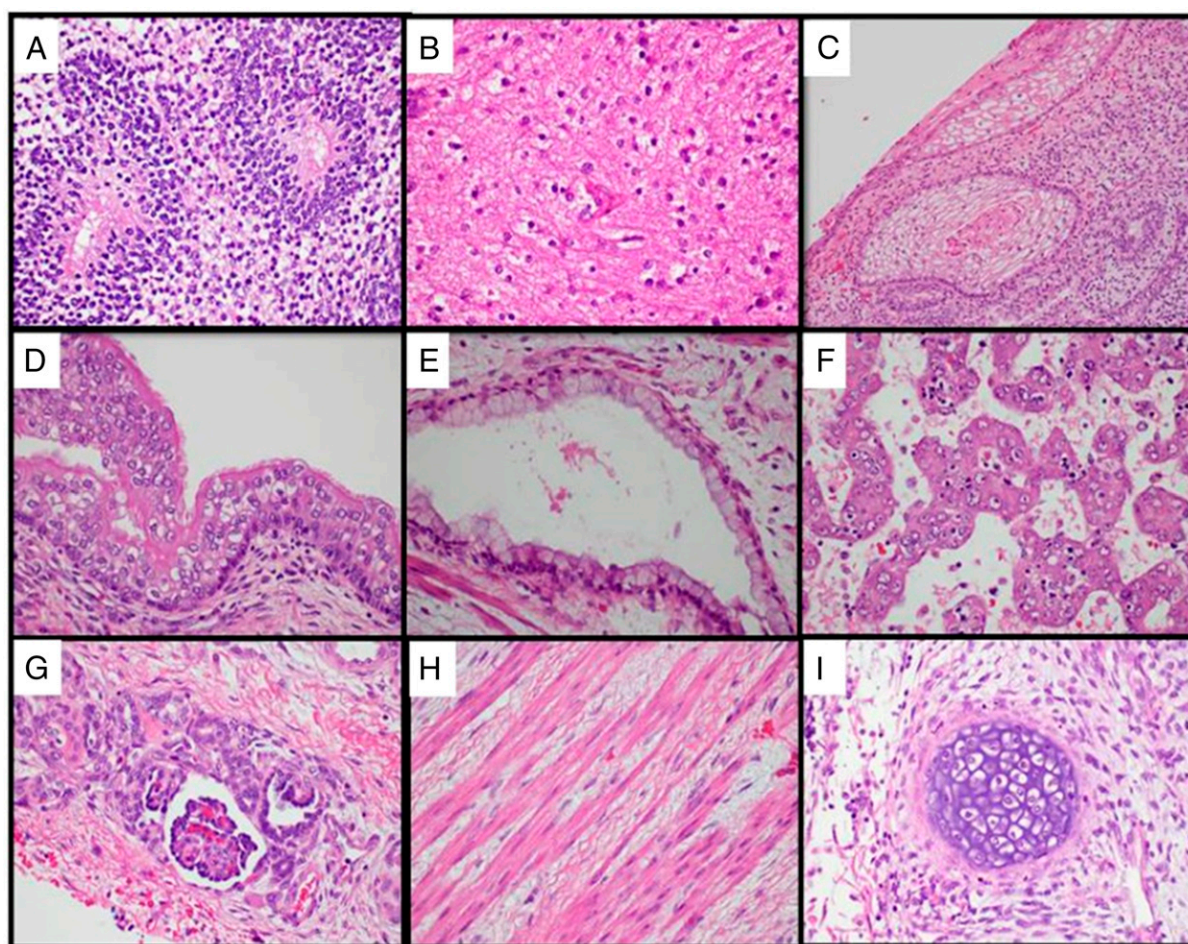


Figure 4. Pathology slides of the sacrococcygeal teratoma. A. Immature neuroepithelium, which defines the teratoma as immature. B. Brain tissue. C. Squamous epithelium. D. Ciliated (respiratory-type) epithelium. E. Mucous epithelium (goblet cells). F. Liver (cords of hepatocytes). G. Kidney (glomeruli and tubules). H. Smooth muscle. I. Cartilage. (All hematoxylin-eosin; $\times 400$ original magnification.)

as improved differentiation and identification of the intrapelvic extension in the mass and any associated anomalies.

The differential diagnosis of SCT includes meningocele; for an anechoic mass, a meconial and mesenteric cyst, ovarian cyst, and hydrocolpos; and for a solid mass, a hemangioma, lipoma, malignant melanoma, and fetus in fetu.

The optimal strategy for managing pregnancies with large SCTs is an area of debate. For large high-risk SCTs, Roybal et al proposed an algorithm for the management of prenatal SCT (4). For fetuses with type I or II SCT, which develop early signs of fetal hydrops before 28 weeks, without signs of impending labor, severe placentomegaly, or maternal complications, fetal surgery is recommended. In patients with contraindications to fetal surgery (type III or IV SCT, cervical shortening) that develop fetal hydrops before 27 weeks, maternal health precedes any fetal intervention. Delivery by cesarean or ex utero intrapartum treatment procedure is recommended for fetuses between 27 and 32 weeks who have high-risk SCT or preterm labor but do not present with hydrops.

Fetal intervention is in the form of a debulking procedure, complete resection of the tumor, or radiofrequency ablation for high cardiac output failure cases.

Many studies have tried using different parameters to predict adverse outcomes in SCT cases. SCT growth rate greater than 61 cm^3 per week was associated with adverse outcomes including death, high output cardiac failure, and preterm delivery. A growth rate greater than 165 cm^3 per week was associated with death. Benachi et al, (5) in a retrospective review of the charts of 44 fetuses with SCTs, showed an association of tumor diameter greater than or equal to 10 cm, fast growth, and high cardiac output failure with higher perinatal morbidity and mortality. Sy et al (6) showed an association of a ratio of solid tumor volume to head volume greater than 1 or a rising ratio with ultrasonographic signs of decompensation, including hepatomegaly, placentomegaly, polyhydramnios, cardiomegaly, ascites, or pericardial effusion. The study also found that the rate of change in the ratio obtained from serial ultrasonography has higher potential to guide management.

At birth, a teratoma size can be large enough to account for 30% to 40% of the neonatal weight. In a retrospective cohort study (7) of 97 fetuses prenatally diagnosed with SCTs between 2000 and 2009, the overall mortality was 26%. The gestational age at delivery was less than 28 weeks in 5 cases, 28 to 31 weeks in 13 cases, 32 to 36 weeks in 27 cases, and more than 37 weeks in 37 cases. The tumor component was cystic in 54 cases and predominantly solid in 32 cases, with mortality rates of 2% and 33%, respectively.

Postnatally, in the absence of prenatal screening, SCT can be visible as a mass at birth. In most cases, neonates with SCT may not have symptoms, and neonatal intensive care may be needed for prematurity, disseminated intravascular coagulopathy, tumor rupture, or high cardiac output failure. The presence of intrapelvic extension may cause urinary obstruction symptoms. Hemorrhagic complications are the most common cause of neonatal mortality.

Postnatal management of an SCT is typically resection of the mass together with the coccyx. An abdominal-perineal approach is recommended for masses with pelvic extensions. Malignant SCTs have generally been treated with surgery and chemotherapy, though some series have suggested that surgery alone may be an option for early-stage malignant SCT. (8) The long-term survival for SCT resected soon after birth is 92% to 95%. (1)

Long-term follow-up of these patients with ultrasonography, serum markers, and physical examination is essential for detecting recurrences (10%–21%) as well as any long-term complications, including fecal or urinary incontinence. Follow-up should be performed every 2 to 3 months for 3 years.

Gabra et al identified 33 patients with SCT between 1977 and 2001. The sacral approach was used in 76% and a combined abdominal and sacral approach was used in 24%. Twenty patients had long-term follow-up, of which 25% reported constipation with soiling and 35% reported urinary incontinence. (9)

Risk factors for recurrence are malignant elements at resection margin, not removing the coccyx, and tumor spillage.

Recent studies have postulated that surgically excised SCTs can be a source for human embryonic stem cells.

Our case was unique given the lack of prenatal diagnosis, despite the large size of the tumor (probably due to rapid growth). It also highlights the importance of effective communication between multidisciplinary team members and the parents.

Follow-up

Despite the severity of illness and large volume of blood product transfusion before and at the time of surgery, MRI

of the brain at discharge was normal. The patient was discharged at 38 weeks of age with follow-up with our pediatric oncology department. The patient's last AFP measurement at 7 months of age was 19.2 ng/mL (19.2 µg/L). There was no evidence of recurrent SCT on MRI 7 months after resection.

Lessons for the Clinician

- Despite advanced imaging studies, a sacrococcygeal teratoma (SCT) can still present as an undiagnosed prenatal mass.
- Prematurity can be a further complicating factor in cases of SCTs.
- An excellent multidisciplinary approach to complicated cases can be very effective in achieving desirable outcomes.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical and laboratory features and management of neonatal teratoma in the newborn.

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Case 2: A Large Prenatally Undiagnosed Mass in a Preterm Infant, What Could It Be?

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Index of Suspicion in the Nursery

2 A Neonate Affected by Maternal Pica

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AUTHOR DISCLOSURE Drs Velazquez, Markowitz, Forman, Wightman, Su, and Nafday have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant is born at 38 6/7 weeks' gestation via vaginal delivery to a 23-year-old gravida 3, para 2-0-0-2 woman. On the first day after birth, he is found to have a critically elevated blood lead level (BLL). The infant was tested because of the mother's prenatal history of an elevated BLL. History revealed the mother had ingested soil from her backyard and used ethnic products from a local store (not tested for lead) throughout the pregnancy. The backyard soil was later tested by the New York City Department of Health and Mental Hygiene (NYC DOHMH), which revealed high lead levels. Five months before delivery, the maternal BLL was 10 $\mu\text{g}/\text{dL}$ (0.48 $\mu\text{mol}/\text{L}$). Repeat maternal BLL on postpartum day 2 was 49 $\mu\text{g}/\text{dL}$ (2.3 $\mu\text{mol}/\text{L}$).

At birth, the newborn Apgar scores were 9 and 9 at 1 and 5 minutes, respectively, the birthweight was 3.57 kg, and the length was 50 cm (body surface area of 0.21 m^2). The infant's venous BLL on the first and second day after birth was 78 $\mu\text{g}/\text{dL}$ (3.8 $\mu\text{mol}/\text{L}$). On admission, the infant had unremarkable routine chemistry studies, a hemoglobin of 17 g/dL (170 g/L), and mean corpuscular volume of 90 μm^3 (90 fL).

On the third day after birth, the newborn was transferred from the NICU of an affiliate hospital to our institution for dual chelation therapy with calcium disodium versenate (CaNa_2EDTA) and succimer, as recommended by the Centers for Disease Control and Prevention (CDC) and NYC DOHMH guidelines. Succimer is a chelating agent that has 2 sulfhydryl groups capable of complexing to lead, making it water soluble, and thus increasing the urinary excretion of lead. CaNa_2EDTA is another chelating agent that chelates lead that has taken the place of calcium and promotes its urinary excretion. CaNa_2EDTA was not available initially, so the infant received oral succimer 350 mg/m^2 every 8 hours as monotherapy. On the sixth day after birth, CaNa_2EDTA was started at 1,000 mg/m^2 per day as a continuous infusion for a total of 5 days. A BLL measurement before the initiation of CaNa_2EDTA revealed that the lead level had decreased from 76 $\mu\text{g}/\text{dL}$ (3.7 $\mu\text{mol}/\text{L}$) to 48 $\mu\text{g}/\text{dL}$ (2.3 $\mu\text{mol}/\text{L}$; 37% reduction) while receiving succimer monotherapy. On completion of dual therapy, oral succimer was continued at two-thirds of the initial dose to complete a 19-day course. BLL was 17 $\mu\text{g}/\text{dL}$ (0.8 $\mu\text{mol}/\text{L}$) on day 11 after birth. A test for glucose-6-phosphate dehydrogenase deficiency was normal. A measure of lead's toxic effect, the blood zinc protoporphyrin, was elevated at 274 $\mu\text{g}/\text{dL}$ (4.9 $\mu\text{mol}/\text{L}$). Iron studies revealed ferritin level of 431 ng/dL (968 pmol/L); iron, 37 $\mu\text{g}/\text{dL}$ (6.6 $\mu\text{mol}/\text{L}$);

transferrin, 195 mg/dL (24 μ mol/L); total iron-binding capacity, 244 μ g/dL (43.7); and saturation, 15%.

The infant's condition was monitored with daily bilirubin levels, basic metabolic panels, and urinalyses, as well as biweekly liver function tests to monitor for medication tolerance and side effects. On the 2nd day of treatment with succimer, he developed electrolyte abnormalities of hyperphosphatemia, hyponatremia, hypocalcemia, and hypomagnesemia, for which he received oral supplementation of these elements and his formula was changed to a low phosphorus formulation to reduce phosphate intake. At the time of discharge, these electrolyte abnormalities had resolved and the infant was back to feeding standard term formula. Chelation was well tolerated by the neonate. Breastfeeding continued to be avoided because maternal BLL was elevated to more than 40 μ g/dL (1.9 μ mol/L).

The BLL rebounded to 28 μ g/dL (1.3 μ mol/L) on day 22 after birth (day 20 of succimer). The patient was discharged from the hospital to complete the course of succimer as an outpatient.

DISCUSSION

Current guidelines from the CDC and the NYC DOHMH recommend dual drug therapy for treating children with a BLL greater than or equal to 70 μ g/dL (3.3 μ mol/L). (1)(2) However, the infant described herein was first treated solely with succimer because CaNa_2EDTA was unavailable. Because of the high price of CaNa_2EDTA , the treating institution and 14 surrounding hospitals no longer provided this option. However, monotherapy with succimer has been used to successfully treat moderate to severe lead poisoning in children in resource-poor countries and did provide some benefit in this case. (3)

The fetus is at risk of lead toxicity from the mother because of the passage of lead across the placenta. (4) After birth, the main portals of entry into the body are via ingestion or inhalation and, very rarely, transdermally. Lead is primarily excreted through the gastrointestinal and urinary systems. Nonexcreted lead primarily accumulates in the bone, but is distributed to all tissues in the body, affecting the hematologic, renal, and neurologic systems.

Lead toxicity occurs by interference with the function of metalloproteins when it substitutes for essential metals such as calcium, iron, and zinc. Its effect on the developing nervous systems is believed to occur through interference with neurotransmission at the synapse (dopamine and acetylcholine) and interference with cell adhesion molecules. In disrupting the intercellular junctions, it increases permeability, leading to a weaker blood-brain barrier. This increases intracranial fluid

accumulation and intracranial pressure, which eventually leads to tissue ischemia and atrophy. (5) In bones, lead alters the activity of osteoblasts through calcium-binding protein synthesis as well as vascularization of new bone and cartilage mineralization. (4) In the kidneys, it particularly affects the proximal tubules, resulting in proteinuria, glycosuria, and decreased calcitriol synthesis, thereby further impairing calcium absorption. Lead is a potent inhibitor of multiple enzymes in the heme synthesis pathway, resulting in the accumulation of potentially toxic precursors and leading to normocytic and microcytic variants of anemia. (4)

Diagnosis and Evaluation

Lead poisoning is often diagnosed with the finding of an elevated BLL. A complete blood cell count should be checked to assess for anemia. Checking for levels of erythrocyte protoporphyrin is a pertinent test for severe lead toxicity; levels generally begin to rise when the BLL is more than 20 μ g/dL. Other causes of an elevated protoporphyrin level include iron deficiency and inflammatory disease. Ferritin levels should also be checked to assess for adequate iron stores. Long bone radiography may reveal dense lines at the metaphysis after prolonged or chronic exposure, but such studies are rarely needed for diagnostic purposes.

Treatment

Of the 4 steps for lead treatment, the first 3 are universally applicable: 1) eliminate the source of exposure; 2) stop the pathway into the body; 3) maximize optimal nutrition of essential metals especially calcium and iron. Iron deficiency is associated with increased lead absorption, retention, and toxicity. Both iron deficiency and lead toxicity affect brain development independently and the combination may be synergistic. Moreover, iron-deficient children excrete less lead in response to a chelating agent for any given BLL compared with iron-sufficient children. However, dimercaprol, which is a congener of succimer, forms a toxic chelate with iron; therefore, iron therapy should be avoided during chelation with dimercaprol. Presumably, decreased lead may be excreted when succimer and iron treatment are given concomitantly.

For a fetus, treatment requires reducing maternal BLL or inducing delivery of the infant. Chelation therapy is the fourth step and is reserved for children with BLLs greater than or equal to 45 μ g/dL (2.1 μ mol/L). The 3 most commonly used chelation drugs in the United States are succimer, CaNa_2EDTA , and dimercaprol. A fourth, weak chelating agent, penicillamine, is used in resource-poor countries when the preferred drugs are unavailable.

Succimer is administered orally and is the initial drug of choice. CaNa_2EDTA can be administered as an infusion or

intramuscular injection, and requires careful monitoring for subsequent renal impairment and hypercalcemia. It can be added to succimer for children with BLLs greater than or equal to 70 $\mu\text{g}/\text{dL}$ (3.4 $\mu\text{mol}/\text{L}$) or as a substitute for succimer when it is not tolerated. Dimercaprol can only be given intramuscularly. It is more toxic than the other drugs and has fallen into disuse. In the present case, only 1 agent was initially available and the decision to proceed was predicated on concern for ongoing toxicity from such high BLLs and any delay in therapy. Three days of solo therapy reduced the BLL significantly. A greater reduction in BLL was subsequently achieved during dual drug treatment. A rebound in BLL was evident soon after completion of the course of CaNa_2EDTA while the infant was still receiving succimer, perhaps indicating that bone lead stores were still substantial. Furthermore, we did not identify a cause for the electrolyte abnormalities because they are not normally associated with either lead poisoning or chelation in the absence of renal disease.

Prevention

Some women develop behaviors related to pica during pregnancy. Although the cause for this behavior is not known for certain, it is speculated that it may be related to iron deficiency as the body attempts to obtain vitamins or minerals that are missing from the mother's diet. In other instances, it may even be related to physical or mental illness. In New York State, obstetrics providers are mandated by the department of health to perform a risk assessment for lead exposure in pregnant women. It is the provider's choice whether to use a risk questionnaire or to proceed directly to BLL measurement. A positive risk assessment should also result in a BLL measurement. For children, as of 2012, the CDC has determined that a BLL greater than or equal to 5 $\mu\text{g}/\text{dL}$ (0.24 $\mu\text{mol}/\text{L}$) is the reference level for identifying the 2.5% of children younger than 5 years with the highest BLLs. It is not a toxicologic threshold; that has yet to be discovered. Rather, it is the point at which primary care physicians are encouraged to assess for sources of exposure, give guidance to prevent lead poisoning progression, and initiate treatment intervention. It is important to note that chelation therapy does not reverse the cognitive effects of toxicity. As the pregnant woman is carrying a potential child, it is reasonable to use the pediatric standard in the interpretation of maternal BLLs and the approach to treatment.

Lessons for the Clinician

1. Early recognition of lead exposure can lead to earlier testing/treatment, thereby potentially minimizing lasting negative health effects.

2. Foreign-born women who have immigrated to the United States may have a distant exposure to lead years before conception. This may be a significant factor contributing to elevated blood lead levels. (6) Because lead can be stored in bone for decades, it can be mobilized into the blood when calcium needs increase in pregnancy.
3. Delaying conception, lead chelation, and calcium supplementation in affected women can decrease fetal exposure. (7)
4. Lead toxicity can have devastating lifelong consequences, making identification of patients or populations at risk of utmost importance. Thus, monitoring maternal lead level in high-risk situations is helpful for recognizing fetal and, later, neonatal lead poisoning.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects on the fetus and/or newborn infant of exposure during pregnancy to environmental agents (eg, mercury, pesticides, etc)

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Case 2: A Neonate Affected by Maternal Pica

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Index of Suspicion in the Nursery

1 A Neonate with Severe Pallor

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ANTENATAL AND BIRTH DETAILS

A female infant is born to a 28-year-old, gravida 2 woman in a nonconsanguineous marriage. The mother had a history of 1 prior miscarriage at 3 months of gestation. The antenatal period during this current pregnancy had been uneventful. The infant is delivered at 37 completed weeks of gestation via emergency cesarean section in view of decreased fetal movements and nonreassuring fetal heart tracings. There is no history of bleeding per vaginum before delivery and the amniotic fluid is clear at the time of delivery. The neonate cries immediately after birth and has Apgar scores of 7, 8, and 9 at 1, 5, and 10 minutes after birth, respectively. The placenta weighs 410 g and is normal on gross examination without any retroplacental clots. There is no family history of recurrent blood transfusions, leg ulcers, gallstones, or abdominal surgeries.

PRESENTATION

Immediately after birth, the infant is noted to have severe pallor and respiratory distress. She is transferred to the NICU, and mechanical ventilation is started in view of the severe respiratory distress. At the time of admission, the infant has a heart rate of 178 beats/min, respiratory rate of 70 breaths/min, temperature of 97.7°F (36.5°C), oxygen saturation of 88% on respiratory support with labiality, and blood pressure of 86/50 (mean 62) mm Hg. On examination, the infant's weight, length, and head circumference are 2,860 g (52nd percentile), 48 cm (57th percentile), and 33 cm (52nd percentile), respectively. The infant has severe pallor, but no cyanosis, icterus, edema, or facial dysmorphism; skin lesions; limb abnormalities; or genital abnormalities. Respiratory distress presents as tachypnea, retractions, and nasal flaring. Cardiovascular examination reveals loud second heart sound with a soft systolic murmur and hyperdynamic precordium. On abdominal examination, the liver is palpable 2 cm below the costal margin and the spleen is not palpable.

EVALUATION

On evaluation, the infant has a hemoglobin concentration of 4.2 g/dL (42 g/L) and packed cell volume of 14%. Both the mother and neonate are blood group O positive; the infant's platelet count is $1.9 \times 10^3/\mu\text{L}$ ($1.9 \times 10^9/\mu\text{L}$) and white blood cell (WBC) count is $23,100/\mu\text{L}$ ($23 \times 10^9/\text{L}$; corrected WBC $15,930/\mu\text{L}$ [$15.9 \times 10^9/\text{L}$]) with 56% polymorphonuclear leukocytes, 38% lymphocytes, and 4% monocytes. Peripheral smear shows anisopoikilocytosis with macrocytes, tear drop cells, schistocytes, and polychromia with abundance of nucleated red blood cells and a reticulocyte count of 20%. Direct Coombs test result is negative. Sepsis

AUTHOR DISCLOSURE Drs Dargu, Kallem, Patil, Subramanian, and Murki have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

screen is normal and blood culture shows no growth of organism. Liver function test shows a total bilirubin of 1.3 mg/dL (22.2 μ mol/L), aspartate aminotransferase 64 U/L (1.07 μ kat/L), alanine aminotransferase 24 U/L (0.4 μ kat/L), total protein 5 g/dL (50 g/L), and albumin 2.9 g/dL (29 g/L). Arterial blood gas at the time of admission shows a pH of 7.37, P_{CO_2} 10.3 mm Hg (1.37 kPa), P_{aO_2} 206 mm Hg (27.4 kPa), and base excess -19.8 mmol/L. Two-dimensional echocardiography performed 4 hours after birth reveals dilated right atrium, right ventricle, severe tricuspid regurgitation with a pressure gradient of 68 mm Hg, biventricular dysfunction, and a duct of 2 mm suggestive of severe pulmonary arterial hypertension. Neurosonography findings are normal. Abdominal ultrasonography findings are normal and there is no bleeding in the internal organs.

PROGRESSION

The infant is started on respiratory support (mechanical ventilation), intravenous fluids, and inotropes. Emergent blood transfusion (20 mL/kg) is given in view of the severe anemia. Pulmonary hypertension improves over 72 hours, extubation is performed 47 hours after birth, and the infant receives oxygen for the next 2 days. The infant starts tube feeding on day 2, progresses to spoon feeds, and direct breastfeeding on day 5. Her hemoglobin concentration improves to 13.6 g/dL (136 g/L) after another blood transfusion of 10 mL/kg after an interval of 24 hours from the first transfusion. One investigation report at this stage reveals the diagnosis.

DIAGNOSIS

Severe anemia at birth with no evidence of jaundice or splenomegaly is suggestive of blood loss. Absence of Rh or ABO settings and negative direct Coombs test result ruled out immune hemolysis. High reticulocyte count and the peripheral smear are suggestive of acute blood loss. In the absence of cord accidents and retroplacental clots, clear amniotic fluid, and normal neurosonography and abdominal ultrasonography findings, a diagnosis of fetomaternal hemorrhage (FMH) is considered. The diagnosis of FMH is confirmed with the Kleihauer Betke test on the mother, which shows abundance of fetal red blood cells (arrows show fetal erythrocytes in Fig) and fetal blood loss of about 180 mL.

DISCUSSION

Fetal blood is likely to enter the maternal circulation in all pregnancies but without any clinical significance in most

cases. Expected fetal blood volume lost is small, with less than 0.025 mL of fetal red cells observed in 75% of cases, less than 0.5 mL in 96%, and less than 15 mL in more than 99%. (1)

The reported incidence of clinically significant FMH varies widely, depending on the volume of fetal blood considered meaningful. Considering the cutoff of 30 mL (amount of fetal blood covered by standard dose of Rh immunoglobulin), the incidence of FMH has been estimated to be approximately 3 per 1,000 live births. (2)

Although numerous risk factors have been described to correlate with the occurrence of FMH, more than 80% of cases with estimated blood loss greater than 30 mL remain unexplained. (2) Various conditions associated with FMH include blunt abdominal trauma, placental abruption, placental tumors, and also obstetric procedures such as amniocentesis, external cephalic version, and manual placental extraction.

The most common antenatal presentation of FMH is decreased or absent fetal movements, observed in nearly one-fourth of all cases. (3) Other less common findings are nonreassuring fetal heart tracings, sinusoidal pattern, fetal hydrops, and fetal growth restriction. (3) Most common postnatal presentation is unexplained anemia in the neonate.

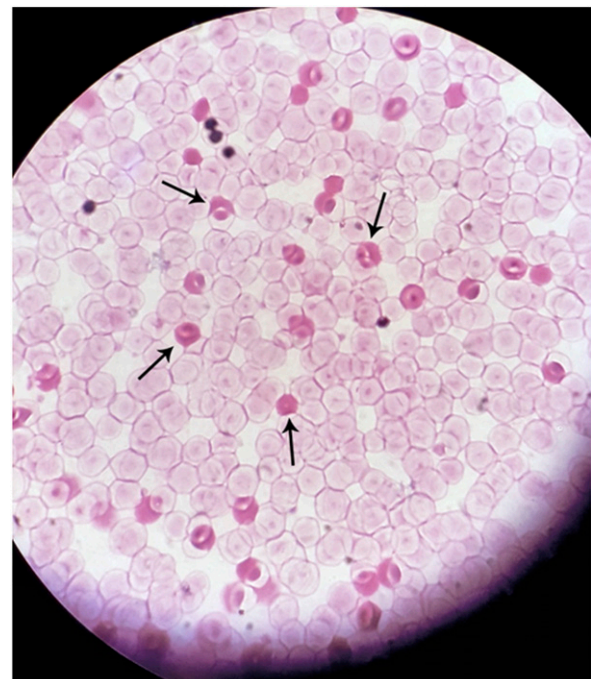


Figure. Abundance of fetal red blood cells seen in the mother's blood specimen (arrows).

The diagnostic tests available for establishing the presence of FMH include the Rosette test, (4) Kleihauer Betke test, (5) and flow cytometry. (6) Of these, the Rosette test is a qualitative test and the other 2 are quantitative tests. The Kleihauer Betke test is currently most commonly used and the standard quantitative investigation for FMH. The test is based on the principle that hemoglobin F, a prominent component of fetal erythrocytes, is relatively resistant to acid elution compared with the hemoglobin of adult erythrocytes. So the maternal red blood cells appear clear as ghost cells and the fetal cells appear cherry red in color (arrows show fetal erythrocytes in Fig). These fetal cells are then counted under the microscope and reported as a percentage of adult cells. Although the Kleihauer Betke test is useful in identifying and quantifying FMH, it has its own limitations in the form of time taken for reporting and dependence on the skill of the technician for identifying fetal cells. It may underestimate or overestimate in case of poor staining of fetal cells, decreasing hemoglobin F in fetal cells and the presence of hemoglobin F in adult cells, respectively.

Lessons for the Clinician

- Fetomaternal hemorrhage should be suspected in all neonates presenting with severe anemia at birth.
- Kleihauer Betke test in the mother gives a quantitative estimation of fetomaternal hemorrhage.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the diagnosis and management of maternal/fetal blood loss such as placenta previa, placenta abruption, vasa previa, and maternal-fetal hemorrhage.

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Case 1: A Neonate with Severe Pallor

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Index of Suspicion in the Nursery

2 A Newborn with a Changing Rash

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PRESENTATION

A 39-week-gestation female infant is delivered by a 35-year-old gravida 3 woman. The neonate is born after an uneventful antenatal period, with a birthweight of 3,350 g; she is a product of a nonconsanguineous marriage. The mother has a history of 2 first-trimester abortions in the past. The infant is delivered via cesarean section in view of meconium-stained amniotic fluid with evidence of antenatal fetal distress. She is depressed at birth and needs bag and mask ventilation for 1 minute; her Apgar scores are 7, 9, and 9 at 1, 5, and 10 minutes, respectively.

The infant is admitted to the NICU in view of the respiratory distress and perinatal depression. She is cared for under a radiant warmer and needs oxygen support by hood for 3 days, following which, the respiratory distress resolves and the infant maintains saturation in room air.

On day 3 after birth, the infant is found to have multiple maculopapular erythematous rashes along with hyperpigmented nodules or plaques over bilateral upper and lower limbs (Fig 1). There is some desquamation, but lesions show absence of any associated vesicles or pustules. Morphologic findings of the skin lesion do not suggest any specific condition and it is a diagnostic dilemma. A senior dermatology consultation is obtained by the neonatology team. The team considers confluent erythema toxicum, nonbullous impetigo, neonatal herpes, and congenital candidiasis among the differential diagnoses at this point. The mother's genitals are examined again, but no vulvovaginal lesions are noted. Titers are sent for toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH) infections for both the mother and infant, and the infant is started on antibiotics and feeding initiated.

On the eighth day after birth, the lesions progress to become more extensive in distribution and now involve the trunk along with bilateral upper and lower limbs. The lesions change to become vesiculobullous (Fig 2). The distribution of lesions becomes linear streak-like, along the lines of Blaschko (Fig 3). The possibility of an alternate diagnosis is mooted, considering the changing nature of the rash; a skin biopsy is performed.

Hematology evaluation of the infant and mother, including the blood culture and TORCH titers, is not suggestive. The biopsy report received on day 10 after birth reveals bullous lesions in the intraepidermal region, with spongiosis of surrounding keratinocytes. Bullous cavity shows collection of eosinophils with the presence of eosinophilic infiltrates in surrounding epidermis and focal prominence of dermal pigment incontinence (Fig 4). The infant has no seizure activity

AUTHOR DISCLOSURE Drs Pal, Jain, Chopra, and Singh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Maculopapular erythematous rashes with hyperpigmented nodules or plaques over bilateral upper limbs and lower limbs (Day 3).



Figure 2. Extensive distribution of lesions with emergence of vesicles and bullae (Day 8).

during the period of hospital stay, and ophthalmologic examination findings are normal. She is discharged, breastfeeding, on day 16 after birth. Lesions are still present at discharge though they have now been replaced by hyperpigmented brownish macules and papules (Fig 5).

DISCUSSION

Based on the evolving morphology of the lesions and on the subsequent skin biopsy report, a diagnosis of incontinentia pigmenti (IP) is made.

The Condition

IP or Bloch-Sulzberger syndrome is a rare X-linked dominant disorder with an estimated prevalence of 0.2 in 100,000 infants, in which changes in skin and its appendages are

present combined with other organs including the central nervous system (CNS). IP appears almost exclusively in girls and is usually lethal in boys. (1) *IKBK* (previously *NEMO*) is the gene known to be associated with IP. (2)

Skin changes, often the first observed clinical sign of IP, typically occur during the first weeks of age to adulthood along Blaschko lines, (2) typically in 4 stages. Onset and duration of stages vary and the stages may overlap. Not all patients experience all stages. Each stage has characteristic morphologic and histopathologic findings. (3)

- Stage 1 (vesiculobullous stage): This stage presents within the first 2 weeks of age in 90% of patients, with erythematous blisters grouped along the lines of Blaschko. Histopathology reveals spongiosis and intraepidermal vesicles containing eosinophils, with many apoptotic keratinocytes in the epidermis.



Figure 3. Change of distribution of lesions to linear pattern along lines of Blaschko (Day 9).

- **Stage 2 (verrucous stage):** This occurs in about 70% of patients usually within 2 months and disappears by 6 months of age. Hyperkeratotic verrucous papules and

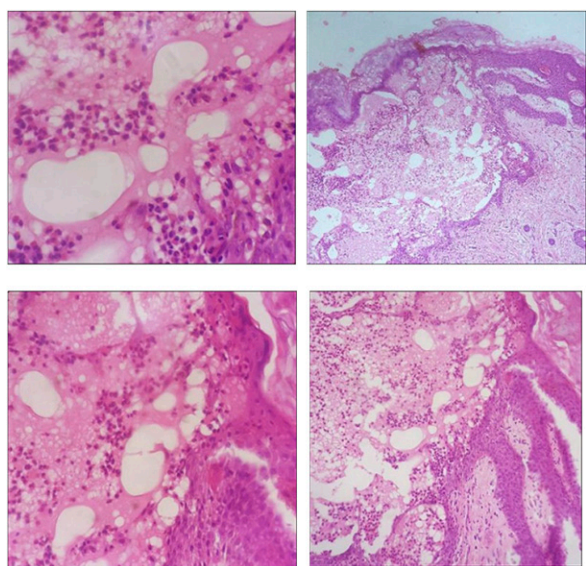


Figure 4. Skin biopsy with bullous lesions in intraepidermal region with spongiosis of surrounding keratinocytes. The bullous cavity is showing collection of eosinophil with presence of eosinophilic infiltrates in surrounding epidermis with focal prominence of dermal pigment incontinence suggestive of Incontinentia pigmenti (Day 9).



Figure 5. Hyperpigmented brownish macules and papules (Day 16).

plaques develop over the healing blisters. Histopathology shows papillomatosis, hyperkeratosis, and acanthosis of the epidermis. Major melanin incontinence is seen in this stage.

- **Stage 3 (hyperpigmented stage):** This is the hallmark of IP, experienced by nearly 98% of patients. Pigmentation ranges from blue-grey to brown, occurs in streaks or whorls, develops within the first few months of age, and fades by adolescence. Marked melanin incontinence, numerous melanophages in the dermis, no epidermal hyperplasia, and scattered apoptotic cells in the epidermis are some of the characteristic histopathologic findings.
- **Stage 4 (atrophic/hypopigmented stage):** This occurs in adolescence and persists into adulthood. It can be identified by pale, hairless patches or streaks found mostly on the lower legs. An atrophic epidermis can be seen with massively reduced melanin in the basal layer, with persistence of apoptotic bodies in the epidermis or papillary dermis. On biopsy, pilosebaceous units and eccrine glands are completely absent at this stage.

Diagnosis

Criteria for the diagnosis of IP were listed by Landy and Donnai in 1993. (1) Skin manifestations in IP represent the

major criteria for its diagnosis. Our patient had 2 major criteria for diagnosis of IP. An update to these diagnostic criteria was proposed in 2014 by Minić et al, (4) who suggested including genetic testing and histopathologic findings as additional diagnostic criteria, along with many others. Genetic testing could not be conducted in our case.

Monitoring and Follow-up

The disease progresses to affect several organs including the skin and hair, CNS, eye, oral cavity, and teeth. CNS anomalies are the most serious complications of IP. (5) CNS anomalies may also manifest from the neonatal period up to early infancy. (6) According to serial reports, 13% to 35% of patients with IP had CNS anomalies in the form of seizures, motor impairment, intellectual disability, and microcephaly. (7)(8)

Lessons for the Clinician

- A rash in the newborn period may have several differential diagnoses, and the prognostic implications for each are different.
- A rash with a changing nature in a neonate should alert the clinician to keep a high index of suspicion for this condition.
- Careful examination of the newborn for the nature, distribution, and progression should be undertaken serially and with relevant laboratory tests to differentiate it from other causes such as impetigo, neonatal herpes, and congenital syphilis.
- A rash in a female infant that occurs in a streak or whorl pattern along Blaschko lines should be considered for IP and a skin biopsy could aid in the diagnosis.
- All neonates with IP may not adhere to the timeline of progression over different stages. The time of presentation of the different stages markedly varies, and an overlap between stages may be noted.
- Once diagnosed with IP, neonates need to receive long-term follow-up to look for abnormalities of other organs.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the differential diagnosis and syndromes associated with hyperpigmented lesions, including cafe au lait spots, Peutz-Jeghers syndrome, giant hairy nevus, incontinentia pigmenti, and pigmented nevi.

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Case 2: A Newborn with a Changing Rash
Somalika Pal, Ashish Jain, Abhishek Chopra and Meeta Singh
NeoReviews 2019;20:e740
DOI: 10.1542/neo.20-12-e740

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Index of Suspicion in the Nursery

1

A Newborn with Absence of Right Forearm, Preauricular Pit, and an Infantile Hemangioma

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AUTHOR DISCLOSURE Drs Reddy Mandadi, Castillo, Mendez, and Rajegowda have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

CASE PRESENTATION

A female infant is born at 35 weeks' gestation to a 19-year-old Hispanic woman and a 21-year-old Hispanic man. The infant has a birthweight of 2,710 g (10th–25th percentile), length of 46.5 cm (10th–25th percentile), and head circumference of 34.1 cm (10th–25th percentile). Apgar scores at 1 and 5 minutes are 9 and 9, respectively. Her physical examination is remarkable for bilateral ear pits, absence of distal two-thirds of the right forearm and hand, and a stump with rudimentary fingers (Fig 1). Good range of motion was observed at the right elbow and shoulder. The left upper extremity and both lower extremities are normal. All her limbs have a good range of motion. No other dysmorphic features are present and the rest of her physical examination findings are unremarkable. A right extremity radiograph shows congenital absence of the right hand, with hypoplastic right forearm bones and a normal right humerus (Fig 2). Her nursery stay is uneventful and the patient is discharged with her mother.

The antenatal period had been uncomplicated and all maternal laboratory test results are unremarkable. Besides polycystic ovarian disease and a missed abortion 1 year before this pregnancy, the mother denies radiation exposure, trauma, medications, or chorionic villous sampling. The family history is negative for congenital anomalies but the father has bilateral ear pits as well. Prenatal ultrasonography at 7, 21, and 33 weeks did not identify any fetal abnormalities. The placental pathology did not show any evidence of amniotic bands.

During the fourth month health supervision visit, a grade II/VI systolic ejection murmur is identified and echocardiography does not show any congenital abnormalities, pointing toward a functional heart murmur. A hemangioma measuring 1×1 cm of the left labia majora is present (Fig 1), with normal external genitalia and anal opening. No genitourinary abnormalities are found on renal and bladder ultrasonography.

A comprehensive metabolic panel and complete blood cell count are within normal limits. Her karyotype is 46,XX. Microarray testing shows absence of heterozygosity, which can be indicative of uniparental disomy. These genomic findings are considered to be of uncertain clinical significance.

At 18 months of age, the patient is growing and developing well and her multidisciplinary care includes genetics, cardiology, rehabilitation medicine, and general pediatrics.



Figure 1. Physical findings seen in our patient. A. Hypoplastic right arm with absence of distal two-thirds of the right forearm and hand, with rudimentary fingers. B. Bilateral preauricular pits that were also present in the patient's father. C. A superficial hemangioma in the vaginal area.

DISCUSSION

Transverse limb defects (TLDs) are rare congenital abnormalities seen in approximately 3.5 to 6.9 per 100,000 births. (1) Most cases are sporadic and not associated with other abnormalities. Skeletal changes are commonly associated with vascular malformations while they are rarely seen in conjunction with hemangiomas. (2) To our knowledge, there has been no report to date of an association of TLD with perineal hemangioma and preauricular pits.

TLD is defined as a partial or complete absence of 1 or more fetal limbs beyond a certain point across the long axis. It is caused by disruption in the apical ectodermal ridge due to insults such as ischemia, bleeding, or chromosomal mutations, during the fourth to eighth week of gestation. One large study showed that the causes include vascular disruption in 35%, genetic factors in 24% of cases, aneuploidy in 6%, and teratogens in 4%, with 32% of cases being sporadic. (1) Other causes include chorionic villus sampling performed before the 10th week of gestation, maternal diabetes, and amniotic bands. Limb defects are not identified on prenatal ultrasonography in 45% of the cases. When multiple malformations are present, cardiovascular and urinary tract anomalies are common in combination with congenital limb defects (37% and 25% of cases), but digestive tract anomalies are significantly associated with congenital limb defects. Rare minor anomalies associated with TLDs include hemangiomas (<1% of cases) and ear malformation (<0.7% of cases). (3) Hemangiomas usually present in the neonate in the first 2 weeks and most commonly involve the head and neck area. Perineal hemangiomas are rare, and their presence should raise the suspicion of an underlying major anomaly. (4)

Multiple anomalies in this patient may be sporadic, vascular, or chromosomal in origin. As previously discussed, the presence of the 3 anomalies seen in our patient is extremely rare, raising the suspicion of a common etiology. Currently,

well-known syndromes such as posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities (PHACE); spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization (SACRAL); and familial angiomatosis were reported initially as incidental findings in patients. This enhances the importance of further evaluation and close monitoring of our patient to identify other probable underlying abnormalities. Besides finding a cause, it is also important to address the consequences of an upper limb defect, including the psychological and physical effect in a developing child.

CONCLUSIONS

TLDs, ear pits, and perineal hemangiomas are commonly known to occur as isolated sporadic anomalies. The presence



Figure 2. A right arm radiograph shows congenital absence of the right hand, with hypoplastic right forearm bones and a normal right humerus. The presence of radii in this patient can rule out other syndromes that present with limb defects.

of major and minor anomalies, should always raise the suspicion of other unidentified abnormalities

Lessons for the Clinician

The differential diagnosis of TLD can be multiple and often includes syndromes with multisystem involvement as follows:

- Thrombocytopenia absent radius syndrome: It is an inherited autosomal recessive disorder characterized by bilateral absence of radii with the presence of thumbs and thrombocytopenia. Hematologic findings may be absent and present within the first few weeks to months after birth.
- Adams-Oliver syndrome: The cardinal features are limb defects and aplasia cutis congenita.
- Fanconi anemia: Most of the cases are inherited in an autosomal recessive pattern. Laboratory findings include thrombocytopenia, macrocytosis, and anemia, but these findings can be absent in one-third of the cases. Absence of radii and hypoplastic thumbs are the most common physical findings.
- Cornelia de Lange syndrome: Despite having upper limb defects such as phalangeal abnormalities or oligodactyly, Cornelia de Lange syndrome is characterized by distinctive phenotypical features and growth restriction.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical features and know how to diagnose and manage congenital anomalies of the upper extremities, such as syndactyly, polydactyly, absent clavicles, absent radius, Sprengel deformity, limb reduction.

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Index of Suspicion in the Nursery

2 A Patient with Trisomy 21, Transient Abnormal Myelopoiesis, and Pneumoperitoneum

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AUTHOR DISCLOSURE Drs Barkhuff, Camacho, McKee, and Stefanescu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 34-week-gestation male infant is born appropriate for gestational age to a 41-year-old gravida 3, para 3 woman. The patient's mother had received limited prenatal care starting at 15 weeks, and is found to have a positive result on maternal serum α -fetoprotein screening test and an amniocentesis that confirms trisomy 21 (47,XY+21 karyotype) with no evidence of translocation or mosaicism. The infant is born at an outside hospital and has physical features characteristic of trisomy 21. He is transferred to our facility for respiratory distress and multiple episodes of apnea and bradycardia on the day of birth. Sepsis is ruled out on admission. His initial complete blood cell count is significant for a white blood cell count of $15,300/\mu\text{L}$ ($15.3 \times 10^9/\text{L}$) with 25% blasts. He is also noted to have an enlarged liver that is 1 cm below the costal margin. Peripheral blood smear and flow cytometry findings are consistent with a diagnosis of transient abnormal myelopoiesis (TAM). Pediatric hematology is consulted and recommends complete blood cell counts which are obtained regularly until day 22 after birth, when the TAM spontaneously resolves.

The infant is able to receive full enteral feedings until he develops abdominal distention and irritability on day 12 after birth. An abdominal radiograph is notable for pneumoperitoneum concerning for an acute bowel perforation without signs of pneumatosis intestinalis (Fig 1). A blood culture specimen is obtained and he is started on antibiotics. A nasogastric tube is placed for gastric decompression while the infant is stabilized with appropriate fluid replacement and is given nothing per mouth. Immediately before surgery, he develops acute cardiopulmonary compromise requiring intubation, mechanical ventilation, and inotropic support. Surgical exploration reveals that the bowel appears viable. There is significant inflammation in the right lower quadrant and fibrinous exudate around the cecum. The appendix appears quite inflamed with an obvious area of perforation (Fig 2). An appendectomy is performed. The histopathologic evaluation of the resected specimen shows neutrophilic exudate (Fig 3). This confirms the diagnosis of acute appendicitis and periappendicitis.

Immediately after surgery, the infant requires multiple normal saline boluses and inotropic support. His blood culture and peritoneal fluid culture are positive for *Escherichia coli* and *Klebsiella pneumoniae*. Cerebrospinal fluid culture and gram stain are negative. He continues to require intubation for 4 days after

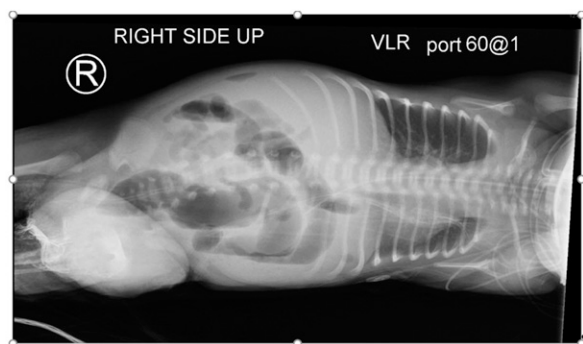


Figure 1. Abdominal radiograph showing gaseous distention of the bowel with free intraperitoneal air on day 12 after birth.

surgery, and gradually weans to low-flow nasal cannula. Feeds are gradually resumed and he achieves full enteral feedings by 28 days after birth. His postoperative course is also complicated by a surgical site infection that develops on postoperative day 7. The infant completes a 14-day antibiotic course. He is discharged from the NICU on day 39 to the general pediatric department to work on oral feedings. He is discharged from the hospital 1 week later on low-flow nasal cannula and full oral feedings with a recommendation to return for pediatric hematology and pediatric pulmonology follow-up as an outpatient. He is seen by pediatric hematology and pediatric pulmonology at 2.5 months' chronologic age and advised to get monthly complete blood cell counts until age 24 months and to gradually wean off nasal cannula oxygen at home during the day. He will continue follow-up with these specialists as an outpatient.

DISCUSSION

Several cases of neonatal appendicitis have been described in the literature with few of them in premature infants. However,

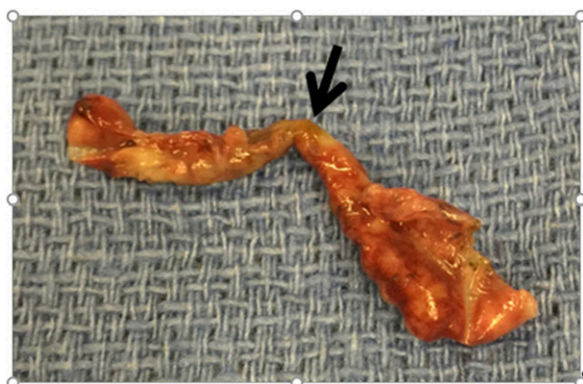


Figure 2. Gross appearance of the appendix showing inflammation and an area of perforation (arrow).

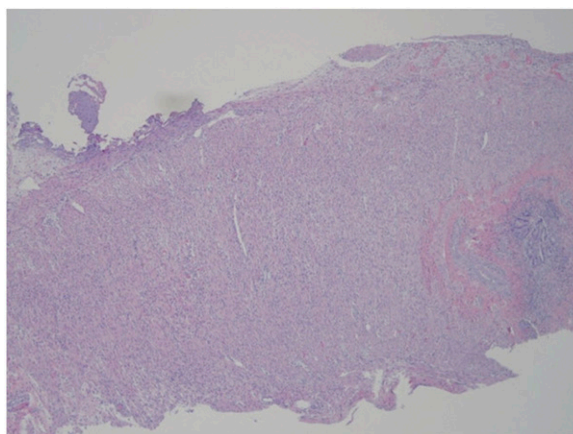


Figure 3. Histopathology slide of the appendix showing neutrophilic infiltration and inflammation.

it is considered to be a rare occurrence, with an incidence of 0.04% to 0.2%. Acute appendicitis is therefore rarely considered in the differential diagnosis of acute abdomen in neonates. However, it is associated with higher morbidity and mortality rates in neonates than in older children. Acute appendicitis in neonates is often associated with prematurity, congenital abdominal defects, cystic fibrosis, or Hirschsprung disease. Neonates may be at low risk for appendicitis for several reasons: the neonatal appendix has a wide opening to the cecum, the diet is liquid, infants are often kept in recumbent position, and infections are generally infrequent.

Other than prematurity at 34 weeks, comorbidities usually associated with neonatal appendicitis were not found in our case. Particularly in the case of preterm neonates, there is debate about whether neonatal appendicitis is actually necrotizing enterocolitis (NEC) affecting the appendicitis or classic appendicitis. In the case of this patient, NEC would be a much more likely diagnosis given the infant's prematurity and the relative incidences of each entity in the neonatal period. However, on surgical exploration, an obvious area of perforation was noted in the appendix and the surrounding bowel appeared normal, supporting the diagnosis of classic appendicitis.

Given the low risk of appendicitis in a patient with trisomy 21 with no risk factors, we wonder if TAM could have predisposed this patient to appendicitis. Lymphoid hyperplasia is known to be the most common pathologic finding associated with acute appendicitis, though it is unclear whether this finding is the cause or effect of acute appendicitis. Development of lymphoid hyperplasia in the periappendiceal region, which could occur during the natural course of TAM, could have caused the obstruction of the appendiceal opening into the cecum with subsequent perforation.

Another unusual aspect of this case is that a decreased incidence of appendicitis has been reported in patients with trisomy 21 compared with the general population, which lowered the index of suspicion for diagnosis.

Lessons for the Clinician

- This may be the first case report of an infant with trisomy 21, TAM, and perforation of the appendix. A search of the literature did not uncover a similar case.
- A perforated appendix in preterm infants is associated with high mortality.
- A possible association between TAM and acute appendicitis may exist in infants with trisomy 21, and therefore, physicians need to maintain a strong clinical suspicion. Early institution of supportive therapies such as appropriate fluid management, gastrointestinal decompression, antibiotic therapy, and surgical consultation and intervention, when necessary, can significantly improve outcomes.

ACKNOWLEDGMENT

Special thanks to Drs Jodi Mayfield and Kathleen Madden for their thoughtful review of this case report.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical manifestations, diagnosis, and management of infants with perforations of the gastrointestinal tract (including gastric and intestinal).

Suggested Readings

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Parent Resources from the AAP at HealthyChildren.org

- **Children with Down Syndrome: Health Care Information for Families:** <https://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Children-with-Down-Syndrome-Health-Care-Information-for-Families.aspx>

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Case 2: A Patient with Trisomy 21, Transient Abnormal Myelopoiesis, and Pneumoperitoneum

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Index of Suspicion in the Nursery

4 A Preterm Infant with a Necrotic Ulcer Over the Perianal Area

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PRESENTATION

A 1.07-kg male infant with severe growth restriction is born at 30 weeks' gestational age to a 36-year-old gravida 3, para 2 mother by emergency cesarean delivery for nonreassuring heart tracing. The parents are of low socioeconomic status and are first-degree consanguineous relatives. The mother received steroids and her membranes ruptured at delivery. At birth, the infant's cord clamping was delayed, and after an initial weak cry he underwent intubation for poor respiratory efforts. Apgar scores were 4 and 7 at 1 and 5 minutes, respectively. His initial stabilization included surfactant administration, mechanical ventilation with volume guarantee, catheter line placement (umbilical venous and arterial catheters), initiation of total parenteral nutrition, antibiotics, and inotropic support. On day 3, he underwent extubation and received noninvasive intermittent positive pressure ventilation (NIPPV), inotropic support was discontinued, and antibiotics were stopped, because his blood culture was sterile. He demonstrated steady clinical improvement in the next 3 days, was weaned from NIPPV to nasal continuous positive pressure, and nasogastric feeds progressed gradually.

On day 6, the bedside nurse noticed a small macule and blister with surrounding erythema over the lateral aspect of his right thigh, which progressed rapidly in hours to blackish-gray discoloration of skin in an area 4 × 1 cm in size with a small hemorrhagic lesion in the center (Fig 1). The infant's clinical condition worsened rapidly in the next 24 hours; he became lethargic, hypothermic, tachycardic, hypotensive with poor perfusion, and apneic with increased oxygen requirement. He underwent elective reintubation for recurrent apnea and mixed respiratory and metabolic acidosis. A limited sepsis screening (complete blood cell count and cultures from blood, skin wound, and urine) was performed. Empiric antibiotic treatment with piperacillin-tazobactam was commenced. The infant received a bolus of normal saline, and dopamine treatment was commenced for low mean blood pressure. Blood investigations revealed the following: hemoglobin 11.01 g/dL (110 g/L); WBC 7,001/ μ L (7.1×10^9 /L); neutrophils 11.43% (absolute neutrophils 0.80); lymphocytes 49.82%; platelet count 91×10^3 /mL (91×10^9 /L), C-reactive protein (CRP) 71 mg/L (675 nmol/L; reference range <10 mg/L [<95 nmol/L]). Serum electrolytes, calcium, magnesium, and renal parameters were normal.

Differential Diagnosis

In view of the rapid deterioration in a previously stable infant with high CRP and absolute neutropenia, a diagnosis of neonatal sepsis with shock was considered. The rapidly progressive necrotic skin lesion with blackish-gray eschar is



Figure 1. Infant's skin on Day 6.

characteristic of an ecthyma gangrenosum (EG), which is pathognomonic of *Pseudomonas* infection. Other differential diagnoses considered were noma neonatorum (NN), pyoderma gangrenosum, necrotizing fasciitis, septic emboli due to other infectious agents, and necrosis secondary to vasoactive medications.

Progression

Within 12 hours, blood culture revealed *Pseudomonas aeruginosa*, reflecting severe high inoculum bacteremia; in addition, swabs from the necrotic lesion and urine also showed heavy growth of the same strain of *P aeruginosa*, which was resistant to aminoglycoside, cefepime, and piperacillin-tazobactam and sensitive to ceftazidime and meropenem. The infant's clinical condition continued to deteriorate in the next 48 hours; blood gas showed persistent metabolic acidosis, with further increase in CRP to 175 mg/L (1,601 nmol/L). He developed a picture of disseminated intravascular coagulopathy. Head ultrasonography showed grade 1 intraventricular hemorrhage. The skin lesion further spread medially to involve the anal and sacral areas (Fig 2).

The infant was transferred to the isolation room, and all infection control measures and contact precautions were initiated. He needed dobutamine, adrenaline, and hydrocortisone to maintain his blood pressure and oscillatory ventilation for poor oxygenation and ventilation. Functional echocardiography guided his hemodynamic and fluid requirement. Based on the culture results, the antibiotics were switched first to ceftazadime and then to meropenem. Blood product support was provided as needed for coagulopathy.

He also received 2 doses of immunoglobulin. Long lines were removed within 24 hours of antibiotic initiation. Lumbar puncture was not performed because of clinical instability. The plastic surgery and wound management teams were involved. Wound care was provided as needed, with hydrogel and silicon foam.

After 3 days of antibiotics and supportive therapy, the infant demonstrated steady clinical and hemodynamic improvement. He made a transition to conventional ventilation after 4 days of oscillation, underwent extubation to NIPPV on day 20 after birth, and was finally weaned off all respiratory support by day 42. Inotropic support was weaned and stopped after 5 days. Repeat blood culture after 1 week was sterile. He received ceftazidime for 5 days and because lumbar puncture could not be performed, meropenem was given for 21 days. The skin lesion started to show improvement by 2 weeks of therapy and resolved completely by 8 weeks with some aesthetic changes due to the deep scar. No surgical debridement was needed (Figs 3 and 4). He did not show any signs of anal stenosis, incontinence, or fistula and was passing stools normally. He was discharged from the hospital on day 53, feeding at will with a discharge weight of 1.9 kg.

DISCUSSION

The Condition

The cutaneous manifestations caused by *Pseudomonas* infection are generally classified as primary and secondary. Primary cutaneous infections involve the skin without systemic infection and occur in immunocompetent patients with



Figure 2. The skin lesion spread to the anal and sacral areas.

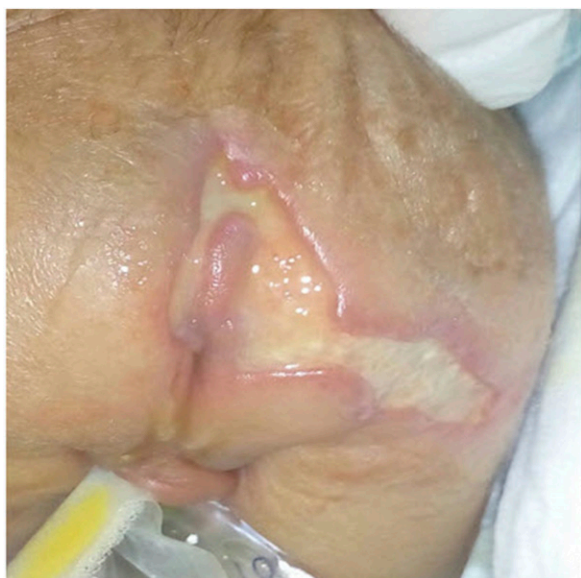


Figure 3. The skin lesion showed improvement by two weeks of therapy.

overall good prognosis. Secondary cutaneous infections occur in patients with severe systemic infection who are immunocompromised, particularly those with neutropenia, and are generally associated with high mortality. (1)

EG is the commonest form of cutaneous manifestation associated with 1% to 3% of severe *Pseudomonas* sepsis. (2) As seen in the current case, it typically begins as a small macule or blister, reddish in color, and rapidly progresses into blackish discoloration of the skin in 12 to 24 hours. When the blister ruptures, it leaves a punched out ulcer covered by blackish eschar surrounded by a light-colored zone with an elevated purplish erythematous external ring (Fig 2). EG histologically shows the preferential infiltration of microorganisms into adventitious and medial layers of the deep vessels (arterioles and venules) without affecting intima, resulting into hemorrhagic occlusive vasculitis. (1) This histologic fact explains why EG typically demonstrates transmural centripetal extension (toward the anus or nasal area)



Figure 4. The lesion resolved completely by 8 weeks with some aesthetic changes due to the deep scar. No surgical debridement was needed.

along perivascular tissue and not a direct hematogenous expansion. The preferred sites for EG are gluteal, perianal, or extremities, and rarely, the face and neck. Traditionally, EG was thought to be caused exclusively by *P aeruginosa* in an immunocompromised host, but recently, EG has been reported in a healthy host as caused by other microorganisms (*Escherichia coli*, *Candida*). A recently published review on EG indicates that *P aeruginosa* was detected in 73.65% of cases; of these, 58.5% had *P aeruginosa* sepsis. (3)

The condition that often gets confused with EG is NN. Noma means cancrum oris, a severe gangrenous lesion involving the mucocutaneous junction of orofacial and rarely anal areas. It was originally described in less developed African and Asian countries in patients with malnutrition and poor hygiene. NN is also predominantly caused by *P aeruginosa* with similar clinicohistologic presentation as EG. The distinctions between NN and EG are not clearly described in the literature. NN predominantly affects the orofacial region and is mainly reported in less developed countries. Some investigators have suggested that NN should be considered the neonatal form of EG. (4) We prefer to call it EG for our case because of the involvement of the perianal area. EG is rare in preterm infants, with very few cases reported in the literature (3 case reports). To our knowledge, this is the first case report from the Middle East of EG with septic shock in a preterm infant caused by multidrug-resistant *P aeruginosa* with complete recovery.

TREATMENT

General Principles of Management

Recognition of EG skin lesion in a preterm infant with neutropenia should alert the physician for the potential of systemic *Pseudomonas* infection. Prompt early anti-*Pseudomonas* antimicrobial therapy will reduce mortality and organ dysfunctions. Coordinated scientific and administrative leadership by the neonatal and infection control teams is essential. The mainstays of management are: 1) implementation of time-sensitive, goal-directed management of septic shock; 2) prevention of horizontal transmission (by isolating/cohorting); 3) identification of any deficiencies in current infection control practices; and 4) surveillance for possible source.

Antibiotics and Wound Care

The Surviving Sepsis Campaign guidelines updated in 2015 suggest that empiric antibiotics should be administered within 3 hours of the identification of severe sepsis. Studies have shown that the odds of death increase with each hour delay in antibiotic treatment. (5) Ideally, an antibiotic should

be administered before sepsis with hypotension sets in, when irreversible organ injury may occur. The current patient received piperacillin-tazobactam as empiric therapy within 1 hour of the identification of EG and meropenem within 18 hours of clinical worsening.

In the era of antibiotic resistance and the shortage of newer antibiotics, selecting monotherapy or combination therapy with antibiotics for suspected or culture-proven sepsis is challenging. The literature is conflicting, and there is a paucity of data for neonates. The recent Cochrane review of 69 trials comparing β -lactam antibiotics alone with β -lactam-aminoglycoside antibiotic combination therapy for sepsis found no significant difference between the groups in all-cause mortality. (6) The review concluded that the addition of aminoglycoside should be discouraged because combination treatment carries a significant risk of nephrotoxicity. Observational studies have claimed the superiority of combination antibiotic therapy for culture-proven sepsis over monotherapy in certain patients (neutropenia, severe sepsis with shock) in special circumstances (infection with multidrug-resistant microorganisms); however, multiple meta-analyses have shown combination therapy to lead to toxicities like fungal infection and nephrotoxicity. (7) In the current case, we used combination therapy for 5 days because of profound shock with absolute neutropenia, and monotherapy for a total of 21 days because we could not rule out associated meningitis. The short course of combination therapy until resolution of shock as guided by functional echocardiography has not been studied in neonates and may improve outcomes as in our case.

Adequate treatment of the local wound of EG is essential for complete recovery. The current patient demonstrated excellent wound healing in spite of a full-thickness wound. Understanding the concept of wound healing is essential for better results. The paradigm of wound management has changed from “dry exposure wound healing” to “moist occlusive wound healing” in the last few years. The traditional gauze dressing is being replaced by the newer occlusive dressing. Dry dressing has the potential of causing pain and damage to the neoepithelium during removal. Newer occlusive dressings create a moist environment, speed up reepithelialization, provide the electrical gradient essential for fibroblast stimulation, promote angiogenesis, and decrease wound infection by decreasing the pH of the wound surface. (8) Most cases of EG require some form of surgical debridement. (3) However, in this patient, the wound care team used hydrogel and silicon foam without any surgical debridement (Fig 4).

Patients with severe septic shock require optimum cardiorespiratory support for better clinical outcomes. This

patient received oscillatory ventilation, fluid resuscitation, multiple inotropic support, hydrocortisone therapy, and intravenous immunoglobulin. Other case reports have suggested that EG might be the initial manifestations of agammaglobulinemia/hypogammaglobulinemia. (3)

Prevention

Our unit follows the infection control practices recommended by the Centers for Disease Control and Prevention and the European Society of Clinical Microbiology and Infectious Disease. These include strict hand hygiene, isolation and contact precaution, active screening of the patient and patient contacts, environment modification and cleaning, and antibiotic stewardship programs. (9)

For better prevention and control, it is imperative to understand the basic behavior of *P aeruginosa* in the NICU setting. *P aeruginosa* is an opportunistic pathogen with minimal nutritional requirement, and usually causes disease in a patient with a weak mechanical defense barrier of skin or one who is immunocompromised. High relative humidity and a moist environment are essential for their colonization and proliferation. (1) Factors that promote growth and act as a reservoir of *P aeruginosa* are hands of health care workers, equipment (incubators with high humidity, respiratory support systems), and a colonized patient and his/her environment (sink and water system, antiseptic solutions, lines and catheters, hubs, intravenous fluids, total parenteral nutrition, and other factors).

Lessons for the Clinician

- Ecthyma gangrenosum should be considered in the differential diagnosis of rapidly progressive necrotic ulcer and can be the initial presentation of *Pseudomonas* sepsis in a preterm infant with neutropenia.
- Early treatment with anti-*Pseudomonas* antibiotics will improve survival in this otherwise devastating disease.
- Newer occlusive dressings provide an optimum environment that will enhance wound healing.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations, diagnostic features, management, and complications of neonatal infections with *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Citrobacter*, *Salmonella*, and *Pseudomonas*.

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Case 4: A Preterm Infant with a Necrotic Ulcer Over the Perianal Area
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Index of Suspicion in the Nursery

3 A Preterm Neonate with Severe Respiratory Distress and Hydrops

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AUTHOR DISCLOSURE Drs Soltys and Harmon have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant is born at an estimated 27+3/7 weeks' gestation via emergent cesarean delivery due to vaginal bleeding and fetal distress. The mother is a 31-year-old gravida 8, para 1-2-4-3 woman with pregnancy complications including absence of prenatal care, premature rupture of membranes, vaginal bleeding, and premature labor. She reports to our hospital on the morning of birth with preterm labor and vaginal bleeding. She receives 1 dose of steroids, magnesium, and antibiotics (ampicillin and azithromycin). Ultrasonography on the day of birth shows left ventriculomegaly, echogenic bowel, and shortened long bones suggestive of skeletal dysplasia.

The infant is apneic on presentation and severely edematous. He requires extensive resuscitation including intubation, emergent UV line placement as well as thoracentesis and abdominal paracentesis because of persistently low oxygen saturations. On admission, examination reveals generalized edema, widely split cranial sutures, and grossly distended abdomen.

Laboratory findings on admission reveal metabolic acidosis, low normal hemoglobin (11.5 g/dL [115 g/L]), alanine aminotransferase of 473 U/L (7.9 μ kat/L), aspartate aminotransferase of 2,837 U/L (47.3 μ kat/L), total bilirubin of 12.3 mg/dL (210.3 μ mol/L), direct bilirubin of 4.7 mg/dL (80.4 μ mol/L), and an albumin of 1.7 g/dL (17 g/L). Coagulation studies show a prothrombin time of 23.8 seconds with international normalized ratio of 2.25 and activated partial thromboplastin time of 38.6 seconds. A radiograph of the chest and abdomen on admission is consistent with hydrops with bilateral pleural effusions and gross superficial edema as well as findings of premature lung disease (Fig 1). This radiograph is also pertinent for broad bands of lucency in the pelvis; however, this is not noted by the radiologist or the primary team at the time. Maternal prenatal screens are sent as well as laboratory tests for infection in the infant, including a culture sample of peritoneal fluid.

DISCUSSION

Diagnosis

The differential diagnosis for hydropic neonates, with or without anemia, is quite broad but should include the following diagnoses (1):

- Hemolytic disease of the newborn
- Congenital glycosylation disorders
- Chromosomal abnormalities
- Turner syndrome
- Congenital tumors, especially teratomas
- Maternal hyperthyroidism
- Maternal diabetes

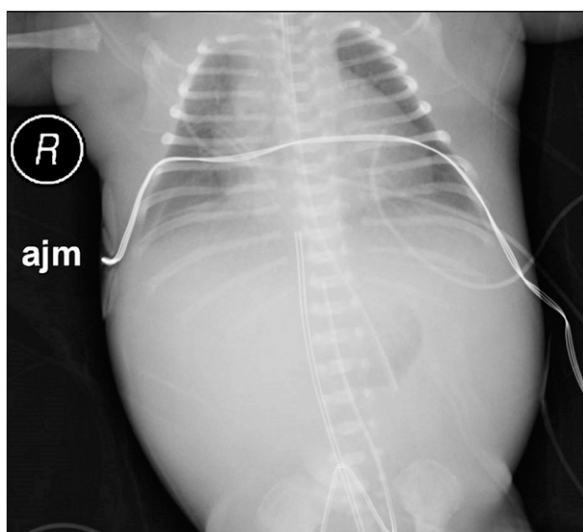


Figure 1. Radiograph of the chest, abdomen, and pelvis showing bilateral pleural effusions, diffuse superficial edema, and broad bands of lucency within the pelvis.

- α -thalassemia
- Fetal cardiac defects
- Various infectious causes including
 - Parvovirus B19
 - Cytomegalovirus
 - Syphilis
 - Human immunodeficiency virus
 - Toxoplasmosis
 - Rubella



Figure 2. Femoral radiograph showing broad bands of metaphyseal lucency in the pelvis as well as a serrated femoral metaphysis, both signs of congenital syphilis infection.

While awaiting laboratory results, several imaging modalities were used to further evaluate this infant. Complete abdominal ultrasonography showed simple ascites throughout the abdomen with echogenic kidneys consistent with acute kidney injury. Long bone radiographs were obtained including one of the femur showing broad bands of metaphyseal lucency in the pelvis with abnormal serration of the femoral metaphysis (Fig 2). Shortly thereafter, maternal prenatal laboratory tests resulted in rapid plasma reagin (RPR) reactive at 1:256. These findings increased our suspicion of congenital syphilis (CS). Subsequently, this patient's syphilis RPR test was reactive at 1:256, confirming a diagnosis of CS.

The Condition

Cases of CS have been increasing in recent years, correlating with the increasing incidence of primary and secondary syphilis in mothers in the United States and several European countries. The overall rate of CS decreased in the United States to a nadir in 2012 to 8.4 cases per 100,000 live births; however, in 2014 the reported incidence increased to 11.6 per 100,000 births. (2) Many of these cases are the result of lack of prenatal care, but there are instances of inadequate treatment as well. *Treponema pallidum*, the bacteria known to cause syphilis, can cross the placenta starting at 14 weeks' gestation. The risk of infection increases with advancing gestational age. (3) If treated with penicillin G at least 30 days before delivery, the likelihood of infection decreases dramatically. (2) Without proper treatment, however, *T pallidum* can cause a congenital infection with a wide spectrum of effects.

Most infants born with CS will not have obvious signs or symptoms at birth. (3) If present, the most common symptoms include syphilitic rash (nonpruritic erythematous macules), jaundice, nasal discharge, and hepatosplenomegaly. (2) The skeletal changes associated with CS are seen in 65% of cases and can include periosteal reactions, osteitis (moth-eaten appearance), metaphysitis (erosions or lucent bands), and pathologic fractures. (4) A small number of cases will result in stillbirths or severe disease, which could include neurosyphilis, hydrops, pneumonitis, pulmonary hemorrhage, or neonatal death. (5)

Whether based on maternal history, physical examination, or radiologic findings, if CS is suspected, treatment with penicillin G is indicated. Regimens include aqueous crystalline penicillin G 100,000 to 150,000 units/kg per day, administered as 50,000 units/kg per dose intravenously every 12 hours during the first 7 days after birth and every 8 hours thereafter for a total of 10 days or procaine penicillin G 50,000 U/kg per dose intramuscularly every day for 10 days. (6) With treatment, many of the pathologic findings, both skeletal and otherwise, should resolve. (4)

Lessons for the Clinician

- With the increasing incidence of congenital syphilis (CS), it is vital to maintain appropriate clinical suspicion for CS.
- Clinicians should appreciate that signs and symptoms of CS can occur on a spectrum, including nonimmune fetal hydrops.
- Physicians should recognize the appropriate evaluation and treatment of CS.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the differential diagnosis and the plan of evaluation and management of a fetus with nonimmune hydrops.
- Know the clinical manifestations and diagnostic features of perinatal infections with *Treponema pallidum*.

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Index of Suspicion in the Nursery

1

A Rare Case of Antenatal Hemorrhagic Stroke and Recurrent Purpura Fulminans in a Preterm Newborn

Ivy Wei Ling Ang, MBChB, MMed,* Daisy Kwai Lin Chan, MBBS, MMed,*
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CASE REPORT

AUTHOR DISCLOSURE Drs Ang, Chan, Lam, and Shah have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A female infant is born prematurely at 33 weeks of gestation to consanguineous parents (parents are first cousins). The mother has had 2 uneventful pregnancies and both children are well. There is no history of recurrent miscarriages, stillbirth or neonatal stroke, or family history of bleeding diathesis or clotting disorders. Antenatal scans had revealed the fetus to be growing well until 30 weeks of gestation, when the weight dropped from the 40th to the 3rd percentile. At that time, the amniotic fluid volume, Doppler scan, and placental blood flow were normal. The mother had been asymptomatic, with normal blood cell count and erythrocyte sedimentation rate.

Now at 33 weeks of gestation, the mother presents to the emergency department with reduced fetal movements over the previous week. She is admitted for observation. Antenatal ultrasonography confirms the earlier findings of intra-uterine growth restriction and documented normal amniotic fluid volume and Doppler scan. She remains clinically well. However, cardiotocographic monitoring the next day reveals the presence of repeated decelerations suggestive of nonreassuring fetal status, prompting an urgent cesarean delivery.

The infant is well at birth, and has a good cry. Apgar scores are 6 and 9 at 1 and 5 minutes, respectively. Birthweight is 1,160 g (<3rd percentile), length 39 cm (3rd-10th percentile) and head circumference 27.5 cm (3rd percentile). Soon after birth, the infant develops respiratory distress secondary to partially compensated metabolic acidosis (pH, 7.32; partial pressure of carbon dioxide, 19.5 mm Hg [2.6 kPa]; partial pressure of oxygen, 111 mm Hg [15 kPa]; base excess, -12; and bicarbonate, 14 mEq/L [14 mmol/L]). Clinical examination findings are unremarkable and vital signs are normal. No hypoglycemia or electrolyte abnormality is noted. Laboratory investigations on day 1 reveal thrombocytopenia (platelet count $39 \times 10^3/\mu\text{L}$ [$39 \times 10^9/\text{L}$]) and coagulopathy (prothrombin time 60 seconds, activated partial thromboplastin time >180 seconds) in the absence of clinical bruising and external hemorrhage. The hematologic abnormalities are promptly corrected with platelet and fresh frozen plasma (FFP) transfusions. She is empirically treated with intravenous antibiotics because of unexplained thrombocytopenia.

Cranial ultrasonography on day 1 after birth shows bilateral intraventricular hemorrhage with echogenicity in the temporoparietal area. Serial cranial ultrasonography in the ensuing weeks shows progression of hemorrhage, resulting in dilation of both lateral and third ventricles (Fig 1). She appears pale and had tachycardia throughout the first 2 weeks after birth, associated with persistent

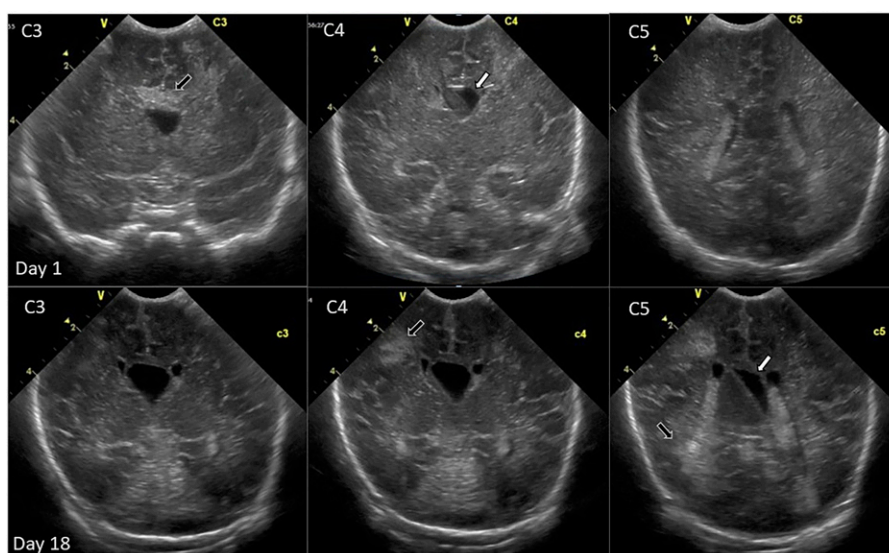


Figure 1. Top row: Coronal section of cranial ultrasonographic images obtained on day 1 after birth. Note the focal hyperechoic area in the anterior aspect of the corpus callosum (black arrow), suggestive of a periventricular bleed. A fluid-fluid level in the cavum vergae (white arrow) indicates intraventricular hemorrhage. Bottom row: Coronal section of cranial ultrasonographic images obtained on day 18 after birth. Note the ventricular dilation (white arrow) and multiple areas of echogenicity in the frontal and parieto-occipital regions (black arrow), suggestive of progression of hemorrhage when compared to previous images.

decline of hemoglobin from 16.6 g/dL (160 g/L) to 9.2 g/dL (92 g/L) despite receiving red blood cell transfusions.

Brain magnetic resonance imaging (MRI) on day 18 after birth shows multiple hemorrhagic lesions (Fig 2). The widespread distribution of affected areas clearly does not correspond to arterial ischemia and suggests the possibility of venous thromboembolism. Amplitude-integrated electroencephalography demonstrates episodes of electrographic seizures that are difficult to control despite multiple phenobarbital boluses. Seizures are finally controlled with phenobarbital 6 mg/kg per day and levetiracetam 80 mg/kg per day.

In consultation with pediatric hematology, thrombophilia screening is undertaken to investigate the etiology of the stroke. The diagnosis of severe protein C deficiency is rendered after an extremely low protein C level of 1% (age-

specific reference range 12%–44%) is found. Protein C level is low in both parents (63% and 49%; adult reference range 70%–140%). Initial management consists of daily FFP transfusions (40 mL/kg per day), which transiently raises the protein C level to 10% but this is poorly sustained. A second MRI/magnetic resonance angiography of the brain on day 44 after birth shows interim development of sagittal sinus thrombosis as well as evolving encephalomalacia (Fig 3). Subcutaneous enoxaparin treatment is commenced on day 50 after birth in view of sagittal sinus thrombosis in the absence of further bleeding. Despite achieving therapeutic anti-Xa levels of 0.5 to 1.0 U/mL, she develops purpura fulminans 10 weeks after birth (Fig 4), which then recurs 20 weeks after birth during an episode of rotavirus gastroenteritis (Fig 5).

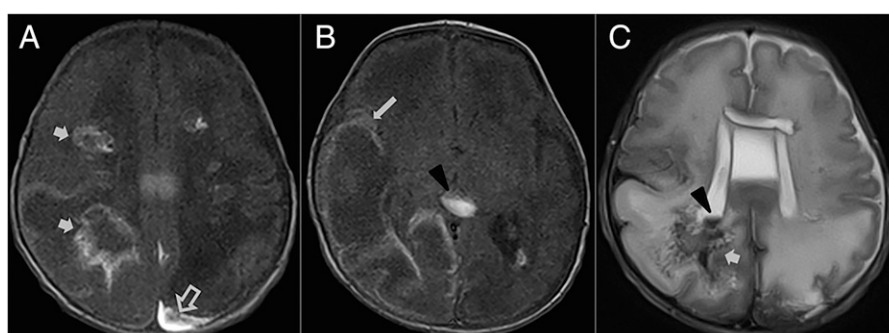


Figure 2. Noncontrast magnetic resonance imaging of the brain on day 18 after birth showing axial T1 (A, B) and T2 (C) sections. Multiple areas of ischemia and hemorrhage can be seen, involving brain parenchyma (thick short arrows), subdural spaces (open arrow), subarachnoid spaces (thin arrow), and intraventricular spaces (arrowheads).

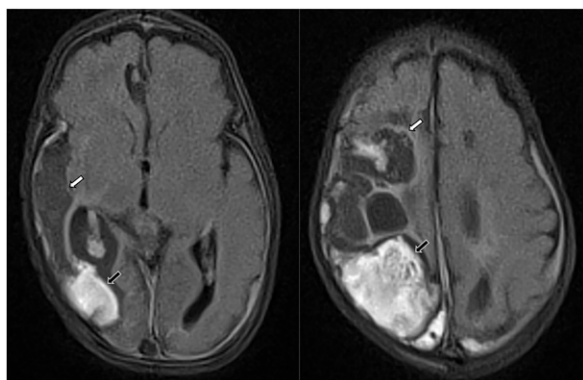


Figure 3. Magnetic resonance imaging of the brain (T1-weighted axial sections) on day 44 after birth showing extensive areas of cystic encephalomalacia (white arrows) and residual products of parenchymal hemorrhages (black arrows), predominantly affecting the right parieto-occipital lobe.

From the third month after birth, there is no further intracranial hemorrhage. Neurologically, the infant has marked head lag and poor truncal tone, with evolving signs of an upper motor neuron impairment involving all 4 limbs. She requires nasogastric tube feeding because of sucking-swallowing-breathing incoordination. Frequent accumulation of oral secretions places her at risk for aspiration.



Figure 4. Necrotic skin lesions (purpura fulminans) over the ventral aspect of the left forearm.



Figure 5. Recurrence of purpura fulminans with necrotic skin lesions over the patient's lower limbs during an episode of rotavirus gastroenteritis.

Her parents receive counseling about the underlying etiology of intracranial hemorrhage and definitive management plans, including the need for long-term replacement therapy with protein C concentrate. Taking into consideration the cost of regular protein C concentrate and the severity of encephalomalacia with high likelihood of poor neurodevelopmental outcomes, a joint decision is made to pursue limited medical care. This consisted of intermittent FFP transfusions, subcutaneous enoxaparin, and physiotherapy.

DISCUSSION

Severe congenital protein C deficiency is frequently diagnosed late or underdiagnosed because of its rarity and variable presentation. A frequent mode of presentation is neonatal purpura fulminans or disseminated intravascular coagulation. (1) It may also be associated with massive thrombosis or in utero death. Case ascertainment often depends on whether mothers with unexplained miscarriage or stillbirth undergo thrombophilia screening. Investigations in cases of neonatal stroke are often not offered because parents are asymptomatic as in the case reported here. Thus, the prevalence of congenital protein C deficiency of 1 in 4 million may be grossly underestimated.

Interpretation of protein C levels in a newborn is fraught with difficulty. Physiologically, newborn infants have low levels of protein C—a term neonate has protein C levels equivalent to 35% of normal adult levels, whereas a preterm neonate has 10% to 15% of normal adult levels, but this has not been universally studied in a preterm neonatal population. (2) Levels are further reduced in the setting of acute thrombosis and hence, thrombophilia screening is usually not advised during such an episode. However, there may be value in testing to exclude severe deficiencies.

In our patient, the declining fetal growth at the 30-week antenatal scan and the paucity of fetal movement from the

32nd week of gestation were red flag features of fetal compromise. Given the severity of the protein C deficiency, it was surprising that she did not initially present with purpura fulminans. We conjecture that the predilection of cerebral vessels for hemorrhage was due to disturbances in cerebral blood flow coupled with intrinsic fragility of the germinal matrix of an immature brain. Also, the presentation of purpura fulminans 10 weeks after birth illustrates that it can occur at any point of the disease process.

With the initial presentation of unexplained metabolic acidosis and thrombocytopenia, clinicians are inclined to investigate for neonatal sepsis first. In retrospect, the paucity of signs to support a diagnosis of sepsis and the presence of severe intraventricular hemorrhagic infarct, out of proportion to the degree of prematurity, would suggest a need to consider alternative etiologies for the thrombocytopenia and acidosis.

There are published recommendations based on expert opinions for initial and long-term treatment of patients with severe protein C deficiency. (3) The standard initial treatment is 10 to 20 mL/kg of FFP every 12 hours until clinical symptoms resolve. Human plasma-derived viral-inactivated protein C concentrate given intravenously has now become available and is the treatment of choice for patients with severe deficiency. (4) In severe protein C deficiency, it is notable that the reported complications are not only thrombotic but also hemorrhagic, reflecting the delicate balance between pro- and antithrombotic forces and the need to approach this with great care. In our patient who developed initial intracranial hemorrhage and later MRI evidence of sagittal sinus thrombosis, the decision to institute procoagulation therapy initially but anticoagulation later was made in consultation with a pediatric hematologist.

The twice-daily FFP transfusions (40 mL/kg per day) produced only a transient rise in protein C levels for our patient. We speculate that the later lack of efficacy might have been related to the highly variable protein C content of each FFP transfusion. Although protein C concentrate is the most reliable source of protein C delivery, this was not started because of the parents' decision to provide limited medical care after having considered the cost and poor neurologic prognosis.

The most widely used long-term treatment is oral anticoagulation to maintain an international normalized ratio in the range of 2.5 to 3.5. Other options such as low-molecular-weight heparin and protein C concentrate administration have been tried with excellent results. Warfarin is the preferred anticoagulant because of its lower cost and ease of administration over the long-term. (5) However, it requires close monitoring and dose adjustment in the initial period, issues that may be problematic for a premature infant with limited blood volume. In consultation with the pediatric hematologist, the patient was given subcutaneous enoxaparin

from 2 months after birth when the intracranial hemorrhage had stabilized, achieving an anti-factor Xa level of 0.5 to 1 U/mL. Enoxaparin was favored over warfarin because

- 1) protein C levels cannot be reliably measured in patients receiving warfarin,
- 2) enoxaparin minimizes the need for routine blood tests,
- 3) there is a risk of warfarin-induced skin necrosis, (6)
- 4) there are reports of drug-drug interactions between antiepileptic drugs and warfarin, and
- 5) there are concerns of future interaction with food.

Monitoring D-dimer levels was said to be useful to confirm the adequacy of anticoagulation. (4)(7)

Although the predominant pattern of inheritance is autosomal dominant, autosomal recessive forms have been reported. The patient in this report was likely to be of the latter type because of parental consanguinity and the assumption that they had 12.5% genes in common. Genetic testing is vital for risk counseling in future pregnancies. Although the parents declined this on the basis of having completed their family, there remains a role for screening siblings of the proband to provide opportunity for genetic counseling.

In conclusion, we recommend that newborns with hemorrhagic cerebral infarcts or thrombosis be screened for hereditary thrombophilias including protein C deficiency, especially in cases of parental consanguinity or when the severity of hemorrhage is out of proportion to the degree of prematurity. It is difficult to achieve adequate protein C levels without protein C concentrates, which is expensive and not easily available in many countries. The challenges in decision making regarding anticoagulation in the presence of hemorrhage and the complexity of care required are best managed by a multidisciplinary team for optimal outcomes.

Acknowledgments

A special thank you to Dr Wendy Liew Kien Ming for giving neurology input for this case report, and also to Dr Sarat Kumar Sanamandra for his radiology input on the imaging studies conducted for this patient.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and pathophysiology of congenital and acquired thrombotic disorders.
- Know the clinical and laboratory features, management, and potential adverse effects of treatment of congenital and acquired thrombotic disorders.

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Index of Suspicion in the Nursery

3 A Rare Cause of Respiratory Distress and Excessive Salivation in a Term Infant

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PRESENTATION

A female infant is born at 39 weeks' gestation via normal vaginal delivery to a 22-year-old primigravida woman. The woman's pregnancy had been uncomplicated. Antenatal ultrasonography findings are normal. Results of her perinatal toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH) infection tests are negative, and group B *Streptococcus* screening result is negative. The membranes rupture just before delivery. Significant finding at delivery includes a meconium-stained amniotic fluid. The infant is vigorous at birth, with Apgar scores of 7 and 9 at 1 and 9 minutes, respectively, and a birthweight of 3,550 kg. She is sent to the normal nursery with her mother in good condition; 2 hours after birth, she develops respiratory distress with desaturation, and is immediately transferred to the NICU for further evaluation and treatment.

The infant is given continuous positive airway pressure of 5 cm H₂O. Fraction of inspired oxygen (Fio₂) is 50%; temperature 36.8°C; heart rate 130 beats/min; respiratory rate 70 breaths/min; and oxygen saturation 94%. Her blood pressure is 73/49 mm Hg.

On physical examination, she is awake and alert, has no dysmorphic features, and chest examination shows respiratory distress with intercostal retractions and diffuse inspiratory and expiratory wheezing. She is also noted to have excessive salivation. No significant organomegaly is found on abdominal examination, and the rest of the systemic examination findings are within normal limits. A blood culture specimen is obtained, and empiric treatment is started with ampicillin and gentamicin. Initial blood gas measurement reveals respiratory acidosis: pH 7.18, Pco₂ 69 mm Hg (9.18 kPa), and bicarbonate 25 mEq/L (25 mmol/L); radiography reveals proper lung inflation and no lung opacities (Fig 1). Over the next hour, she continues to require oxygen to maintain her oxygen saturation above 90%. She develops severe respiratory distress and worsening of the respiratory acidosis on blood gas measurement (pH 7.14, Pco₂ 78 mm Hg [10.3 kPa], bicarbonate 26 mEq/L [26 mmol/L]). She undergoes intubation and receives mechanical ventilation. After intubation, her blood gas measurements improve and radiography reveals no significant changes; the endotracheal tube (ETT) is in a good position (at a depth of 8.5 cm) (Fig 2), but clinically she is noted to have persistence of deep subcostal retraction and diffuse wheezing. Her

AUTHOR DISCLOSURE Drs Alallah, Alkhotani, Baslaim, and Darwich have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

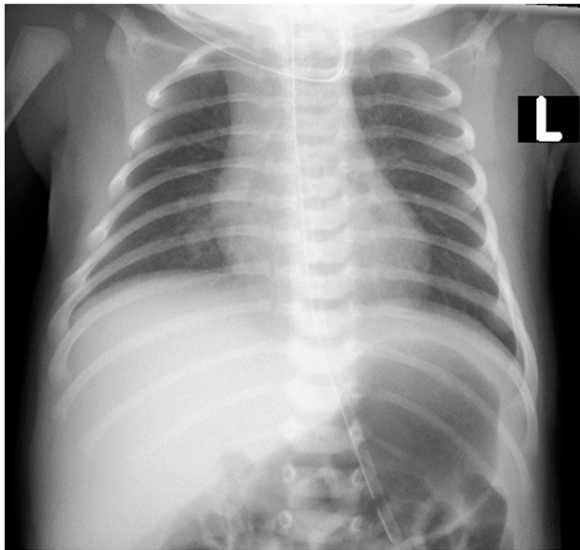


Figure 1. First chest radiograph with the patient receiving continuous positive airway pressure revealed proper lung inflation and no lung opacities.

oxygen requirement is increased to 100% to keep saturation above 94%, increased sedation is tried with no improvement, and the infant undergoes reintubation. Clinically she improves after reintubation with better work of breathing, resolution of subcostal retraction and

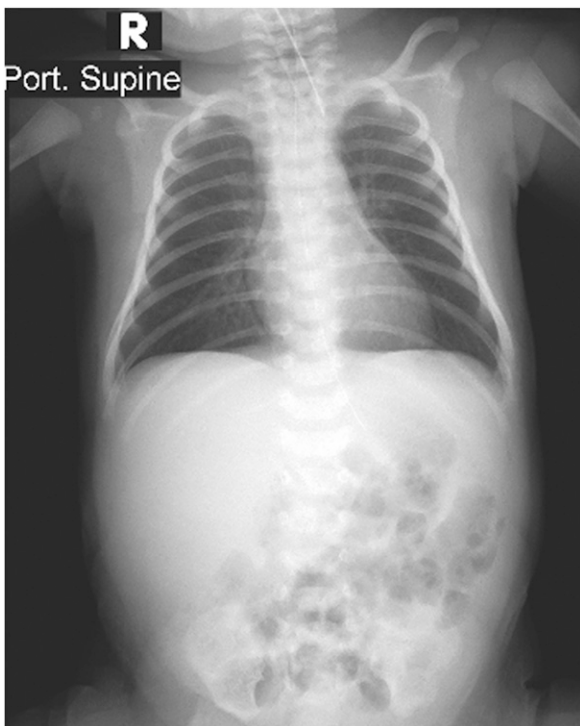


Figure 2. Proper lung inflation and no lung opacities noted after intubation.

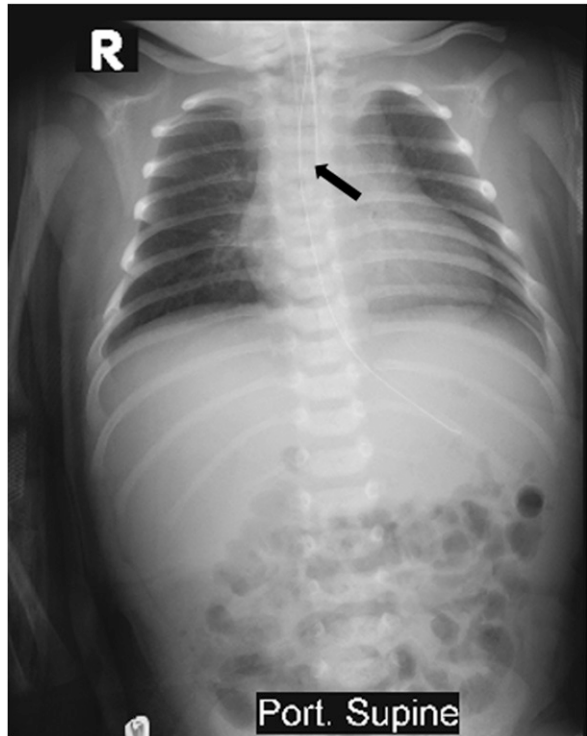


Figure 3. Proper lung inflation and deep endotracheal tube (arrow) noted after intubation.

wheezing, and significant improvement in oxygen saturation (FiO_2 21% and saturation 100%); follow-up post-reintubation radiography reveals deep ETT (at a depth of 10 cm, just above the carina; Fig 3).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute respiratory distress in a newborn with normal radiography findings includes the following:

- Double aortic arch
- Laryngeal web
- Laryngomalacia
- Sepsis
- Subglottic stenosis
- Tracheal stenosis
- Tracheomalacia

CASE PROGRESSION

After reintubation, an attempt to adjust the ETT position resulted in demonstrations of severe respiratory distress and significant desaturation. So the ETT was kept at the level of the carina, which raised the suspicion of airway

obstruction at the level of distal trachea. A cardiologist was called, and echocardiography did not suggest a cardiac abnormality or obstruction.

On consultation, pediatric pulmonology recommended computed tomography (CT) angiography with 3-dimensional reconstruction, which confirmed the diagnosis.

ACTUAL DIAGNOSIS

A diagnosis was made of double aortic arch (DAA) with the right arch more prominent and dominant, and the esophagus and trachea completely encircled (Fig 4). The case was referred to a cardiothoracic surgeon, and surgical repair (Fig 5) was undertaken on day 6 after birth. The nondominant left arch and the patent ductus arteriosus were divided. The patient underwent extubation on the second day after surgery. She started feeding on the third day after surgery, and gradually tolerated full oral intake and was discharged in stable condition 12 days after surgery.

DISCUSSION

DAA is a rare disorder, and it remains an essential element of the differential diagnosis of neonatal respiratory distress.



Figure 4. Computed tomography angiography showed a double aortic arch, with a more prominent and dominant right arch (blue arrow) and a non-dominant left arch (white arrow), and the esophagus and trachea completely encircled.

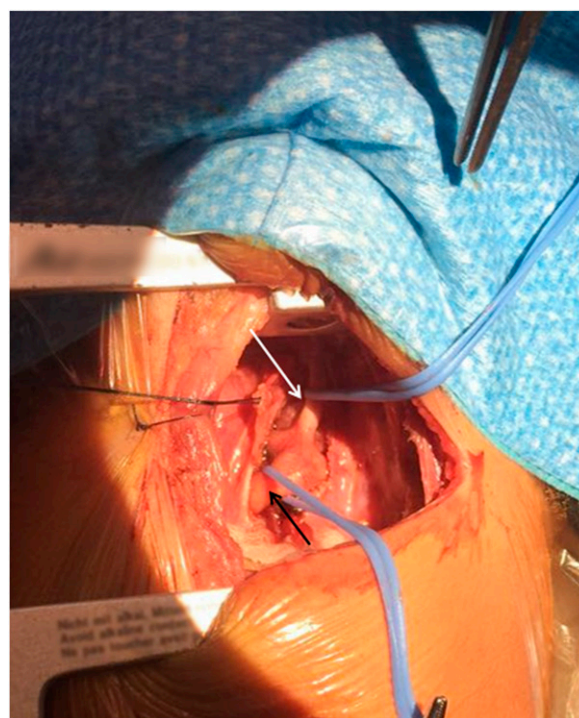


Figure 5. The white arrow is pointing to left subclavian artery (LSCA), and black arrow to the patent ductus arteriosus (PDA). The right arch runs behind the esophagus and trachea and is difficult to visualize. The vessel between LSCA and PDA is the left arch, which is surgically divided.

Congenital heart disease occurs in about 1% of neonates, (1) whereas vascular rings occur in about 1 in 10,000 births. (2) The DAA variants are named based on the size of the aortic arch, with right dominant arch seen more frequently (80%) than left dominant or codominant arches (10% each). (3)

Presentation in the neonatal period is rare, and early diagnosis is difficult because it has a broad clinical spectrum. The mean age at diagnosis for the vascular ring is 6 months. (4) The DAA occurs as a result of failure of regression and persistence of bilateral fourth aortic arches and the dorsal aortic root. (3) Some genetic syndromes are associated with higher rates of vascular rings, including coloboma, heart defects, atresia choanae (also known as choanal atresia), growth restriction, genital abnormalities, and ear abnormalities (CHARGE) syndrome, Down syndrome, and DiGeorge syndrome. (5)

The clinical presentation is related to compression of the esophagus and/or trachea. This can include feeding difficulties, excessive salivation, vomiting, stridor, or respiratory distress.

Evaluation of neonates with respiratory distress often proceeds in a stepwise manner similar to the case presented herein; the clue to tracheal obstruction in the

current case was related to significant clinical and blood gas improvement with deep ETT position, just above the carina, and worsening of the respiratory status after adjustment of the tube position, that is, when the tip of the ETT was placed distal to the obstruction.

The diagnosis was confirmed on CT angiography of the chest. When a definitive diagnosis cannot be made on echocardiography, the definitive management for DAA is a surgical correction through surgical ligation of a duplicated arch. Long-term outcomes for neonates with isolated DAA are excellent. The most common postoperative finding is persistent tracheomalacia, which improves in the first few months of age.

Lessons for the Clinician

- Respiratory distress and excessive salivation at birth or soon after should alert the neonatologists to the possibility of tracheal and esophageal compression by the vascular ring.
- The presence of symptoms after intubation despite the satisfactory position of the endotracheal tube with no lung disease leads to a high index of suspicion. Symptoms of airway compression secondary to double aortic arch may be relieved by placing an endotracheal tube just above the carina, which can be an essential tool to relieve airway obstruction. When echocardiography is unable to diagnose double aortic arch, alternative tools such as computed tomography angiography must be applied.
- Surgical treatment is useful with an excellent prognosis.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the anatomy and pathophysiology (including genetics) of a neonate with an arterial vascular abnormality.
- Recognize the clinical features of a neonate with an arterial vascular abnormality.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a neonate with an arterial vascular abnormality.
- Formulate a differential diagnosis for a neonate with an arterial vascular abnormality.
- Recognize the laboratory, imaging, and other diagnostic features of a neonate with an arterial vascular abnormality.

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Index of Suspicion in the Nursery

1 A Term Infant with Apnea and Stiffening

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AUTHOR DISCLOSURE Drs Arroyo, Fu, and Hufnagel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term male infant born via spontaneous vaginal delivery with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, has an episode of apnea with stiffening and nonsuppressible whole body jerking for 2 minutes, occurring 5 hours after birth. Around 8 hours after birth, he has another episode but with exaggerated startle reflex, lip smacking, and eyelid fluttering. General examination shows no dysmorphic features, and findings are otherwise normal. Initial neurologic examination findings are unremarkable. Continuous electroencephalographic (EEG) monitoring with full neonatal montage is significant for intermittent sharp waves. Over the next day, the infant has 3 episodes of apnea with stiffening and nonsuppressible whole body jerking after each episode. These events are captured but EEG does not show them to be seizures. Initial management with phenobarbital and levetiracetam does not ameliorate spells.

His antenatal course is unremarkable. Family history is remarkable for consanguineous parentage of Middle Eastern descent (parents are first cousins of first cousins). Laboratory evaluation including serum and cerebrospinal fluid studies for infectious and metabolic etiologies shows normal findings. Magnetic resonance imaging (MRI) on day 5 after birth reveals normal brain structure with nonspecific hyperintense basal ganglia signal and minimal subdural hemorrhage from the birthing process. Five days later, findings of a repeat MRI with added spectroscopy are normal.

DISCUSSION

Diagnosis and Further Progress

Given the clinical suspicion for hyperekplexia, the patient was started on a trial of carbamazepine (15 mg/kg per day) and clonazepam (0.05 mg/kg per day) while continuing phenobarbital; with this regimen, he was spell-free for over a week before recurrence. Spells were eventually well controlled with a combination of clobazam (1.3 mg/kg per day) and clonazepam (0.15 mg/kg per day). Spells were acutely managed with the Vigevano maneuver (forcibly flexing legs to the trunk). When the spell did not respond to the maneuver, lorazepam was administered. Serial neurologic examinations revealed increased tone and nonhabituating glabellar reflex with head retraction and spasms elicited by tapping the tip of the nose.

Single nucleotide polymorphism (SNP)-based microarray revealed no pathogenic deletions or duplications. Consistent with first-cousin consanguinity, copy-neutral regions of homozygosity were detected, comprising 9.04% of the genome and containing approximately 127 gene candidates for unmasked recessive

disorders. One of these was *SLC6A5*, located in a 28.3-Mb region of homozygosity (ROH) on chromosome 11p15.1, associated with autosomal recessive hyperekplexia type 3. Next-generation sequencing revealed a novel homozygous truncating *SLC6A5* mutation (c.2077delCinsAAC; p. Leu693Asnfs*12) (NM_004211.3), consistent with disease-causing alleles.

The patient was discharged on nasogastric feeds and progressed to taking all feeds by mouth by 5 months of age. He was evaluated at 13 months of age and still found to have occasional stiffening spells but no myoclonic jerks. His motor development continues to be mildly delayed, with truncal hypotonia and weakness; he is now cruising and taking some steps independently. His spells are controlled with clobazam.

Typical Presentation in Newborns

Hereditary hyperekplexia is a rare movement disorder that manifests shortly after birth. Infants typically have generalized hypertonia while awake, which subsides when asleep. They also develop tonic spasms of the extremities and clenched fists that mimic tonic-clonic seizures. These episodes may lead to apnea and sudden infant death. They

often have feeding difficulties and are at risk for aspiration. A pathognomonic feature is nonhabituation of startle elicited by tapping of the glabella or the philtrum. (1)

Symptoms typically improve during the first few years after birth, with apnea episodes resolving by 2 years of age and hypertonia normalizing by 3 years of age. Developmental delays occur in approximately half of all patients, with fewer having global intellectual disability. Patients may have a wide-based toddling gait that worsens when rushed and lingers until adolescence. (2) The exaggerated startle, however, may persist lifelong and continue to pose a risk of uncontrolled falls. (2)

Management

Clonazepam is the most efficacious treatment reported in cases of neonatal hyperekplexia. (1) In the current case, clonazepam monotherapy was not sufficient to control startle symptoms. Clobazam as monotherapy has been described in the literature with good success in 2 severe infantile cases. (3) Clobazam was added to clonazepam with good results in the current patient, and this combination was also found to be successful in a 7-year-old boy who had significant falls because of exaggerated startle. (4)



Figure. Region of homozygosity (ROH). Single nucleotide polymorphism microarray detected a 15.1-Mb ROH on chromosome 11 (hg19,chr11:7619262-20019858), containing the *SLC6A5* gene (chr11:20,620,946-20,676,610) on chromosome 11p15.1.

SLC6A5 (previously known as *GLYT2*; MIM 604159) encodes a 797-amino acid presynaptic glycine transporter localized to neurons of the medulla, spinal cord, and cerebellum. (5) *SLC6A5* mutations were discovered in patients with recessively inherited infantile hyperekplexia, including increased startle, muscular rigidity, and apnea. Mutations in postsynaptic glycine receptor genes *GLRA1* and *GLRB* are associated with hyperekplexia types 1 and 2, respectively. (6) Genotype-phenotype correlation studies have demonstrated differences between the 3 types of known genetic hyperekplexia. Compared with those with *GLRA1*-associated hyperekplexia, patients with *SLC6A5* mutations more frequently exhibit apnea (80% for *SLC6A5* vs 43% for *GLRA1*) as well as developmental delays (74% vs 39%) and epilepsy (14% vs 5%). (6) Long-term outcome in patients with *SLC6A5*-type hyperekplexia has not been well characterized. Given his age, we are not able to predict the severity of this condition in the current patient, and insufficient cases have been reported to determine whether nonsense mutations confer different disease severity from missense mutations for *SLC6A5*. (6)

A unique aspect of this case is identification of hyperekplexia secondary to mutations in *SLC6A5* as the most likely diagnosis, based on ROH on microarray (Fig). Genomic-based technologies such as SNP microarray allow for detection of copy-neutral ROH in addition to genomic deletions and duplications, not only to determine the extent of interrelatedness, but also to provide a list of candidate genes for unmasked recessive conditions. (7) Quickly obtaining the homozygous intervals increased the certainty of the clinical diagnosis, allowing us to conduct a trial of benzodiazepines before results of the *SLC6A5* gene sequencing were available. This improved control of his symptoms and permitted us to limit further medical and genetic evaluation.

Lessons for the Clinician

- Hyperekplexia may present early in the neonatal period with seizurelike episodes.
- Combination therapy with clonazepam and clobazam may control symptoms.

- Single nucleotide polymorphism microarray elucidates regions of homozygosity that may contain unmasked recessive disease genes with established parental consanguinity.

ACKNOWLEDGMENTS

Drs Charu Venkatesan, Robert Hopkin, Stephanie Merhar, Cameron Thomas, and Mark Schapiro helped diagnose the patient and reviewed the manuscript based on their expertise in neurology, neonatology, and genetics. Dr Teresa Smolarek interpreted the original microarray data, revised the manuscript, and created the figure included with this publication.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the significance of persistent neuromotor abnormalities in infancy (including asymmetries).

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Parent Resources from the AAP at HealthyChildren.org

- Sleep Apnea Detection: <https://www.healthychildren.org/English/ages-stages/baby/sleep/Pages/Sleep-Apnea-Detection.aspx>

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

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Monica S. Arroyo, Ting Ting Fu and Robert B. Hufnagel
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Index of Suspicion in the Nursery

1 A Term Infant with Respiratory Distress

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AUTHOR DISCLOSURE Drs Shridhar, Kumar, and Sodhi have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 38-week, 2,800-g male neonate is born to a gravida 2, para 1 mother with an uneventful antenatal period; the neonate is born via normal vaginal delivery. After a normal transition, he is transferred to the mother's room and begins exclusive breastfeeding. Around 24 hours after birth, in the postnatal ward, the neonate is noted to have tachypnea with poor peripheral pulses and prolonged capillary refill time. Considering the possibility of early-onset sepsis with shock, a 10 mL/kg normal saline bolus is given over 30 minutes and the neonate is transferred to the NICU. Further evaluation shows a respiratory rate of 72 breaths/min, mild intercostal retractions, and heart rate of 150 beats/min, with feeble peripheral pulses and a capillary refill time of 4 seconds. No pallor, icterus, or petechiae are noted, and the cry, tone, and activity of the neonate are normal. The neonate is given oxygen by hood at 3 L/min, intravenous fluids, and intravenous antibiotics.

DISCUSSION

Progression/Diagnosis

Cardiac examination reveals normal first and second heart sounds with a grade 3/6 systolic murmur in the aortic area. Chest radiography (Fig 1) reveals a normal heart size, and 2-dimensional (2-D) echocardiography reveals a critical aortic stenosis (AS) with a left ventricular (LV) ejection fraction of 15% to 20%. Intravenous dopamine injection is started at 10 µg/kg per minute and the neonate is transferred to the cardiac catheterization laboratory for urgent aortic valve balloon dilation.

Management

In the cardiac catheterization laboratory, the diagnosis of AS was confirmed during angiography, which shows severe stenosis at the aortic valve (Fig 2); thereafter, aortic valve balloon dilation was performed using a balloon threaded on the femoral artery guidewire (Fig 3). Repeat 2-D echocardiography performed before discharge revealed mild AS with a gradient of 6 mm Hg, and mild aortic regurgitation with LV ejection fraction of 30% to 35%. The infant was discharged from the hospital with digoxin oral syrup at 10 µg/kg per day and furosemide syrup at 1 mg/kg per day. Follow-up echocardiography after 6 months showed mild aortic regurgitation with LV ejection fraction of 55%.

The Condition

About 10% of all congenital heart diseases are caused by obstruction in the LV outflow tract. In more than two-thirds of cases, AS involves the aortic valve, and



Figure 1. Normal heart size on chest radiography.

less commonly, subvalvular stenosis is involved in one-fourth of cases or supra-ventricular stenosis (6%). "A bicuspid aortic valve with a fused commissure and an eccentric orifice accounts for the most common form of aortic valve stenosis (75%)."⁽¹⁾ Critical AS results from severe anatomic obstruction with accompanying LV failure and/or shock. Patients with critical AS have severe obstruction in utero (usually due to a unicuspid, platelike valve), with resultant LV hypertrophy and, frequently, endocardial fibroelastosis and hypoplasia of the aortic valve and ascending aorta. Infants with critical AS may present in the initial few weeks after birth with signs of poor peripheral perfusion or respiratory distress, which may be mistaken for early-onset sepsis with shock, as we suspected in our index case. (2) The heart murmur may not be prominent because of severe LV dysfunction. The electrocardiogram may be normal in mild stenosis and show LV hypertrophy with inverted T waves in long-standing or severe AS; however, it generally does not correlate with the severity of the lesion. Radiography may

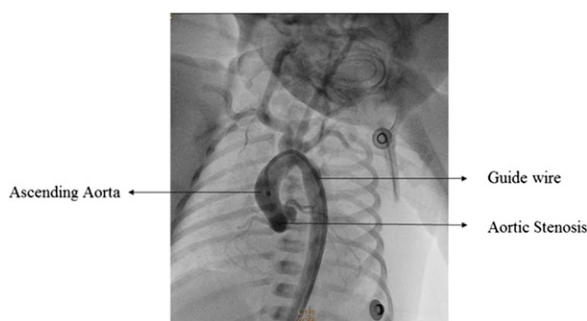


Figure 2. Aortic stenosis on angiography.

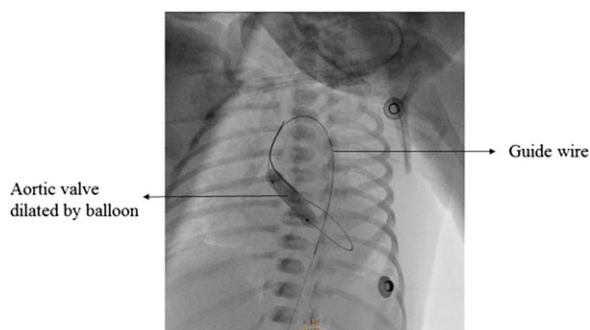


Figure 3. Aortic valve balloon dilation.

show cardiomegaly with pulmonary edema in infants with critical AS. 2-D echocardiography confirms the site and severity of the stenosis. Cardiac catheterization may be needed in some cases; however, it is important to note that the severity of stenosis may be underestimated even on catheterization, because of severe LV dysfunction.

Critically ill newborns with congestive heart failure are stabilized using inotropes such as dopamine, diuretics, and prostaglandin E₁ (PGE₁) to maintain patency of the ductus. (3) In our case, the neonate was immediately transferred for balloon valve dilation and did not require PGE₁. Emergency treatment for infants with critical AS may involve balloon valvuloplasty (or surgery). Percutaneous balloon valvuloplasty is now considered the procedure of choice in many centers. (4) However, bleeding, femoral artery thrombosis, and mitral valve or LV perforation may sometimes occur during the procedure. Surgery is indicated for failure of balloon valvuloplasty in patients with dysplastic aortic valves or if severe aortic regurgitation results. (5) The overall mortality for neonates with critical AS is about 10% in the current era despite the available interventions and is due to associated LV endocardial fibroelastosis in many cases.

Restenosis or regurgitation develops in about one-fourth of patients over time, and annual follow-up examination is recommended after aortic balloon valvuloplasty or surgery. (6) Infective endocarditis prophylaxis is currently only recommended after prosthetic valve replacement.

Lessons for the Clinician

- Consider alternative explanations (other than neonatal sepsis) for respiratory symptoms and poor peripheral perfusion in a neonate.
- Thorough clinical examination (including palpating the peripheral pulses) usually points to the diagnosis.
- Be aware of critical congenital heart diseases presenting in the immediate neonatal period, because they may have been missed on antenatal ultrasound scans.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features of a neonate with a left-sided cardiac obstructive lesion.
- Recognize the laboratory, imaging, and other diagnostic features of a neonate with a left-sided cardiac obstructive lesion.

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Parent Resources from the AAP at HealthyChildren.org

- Common Conditions in Newborns: <https://www.healthychildren.org/English/ages-stages/baby/Pages/Common-Conditions-in-Newborns.aspx>
- When Baby Needs Oxygen at Home: <https://www.healthychildren.org/English/ages-stages/baby/preemie/Pages/When-Baby-Needs-Oxygen-At-Home.aspx>

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Index of Suspicion in the Nursery

3 A Term Newborn with Intrauterine Growth Restriction and Severe Fetal Brain Anomalies

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AUTHOR DISCLOSURE Drs Biobaku, Babata, Friedman, Goddard, and Yen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 29-year-old gravida 4, para 3 woman is seen by the maternal-fetal medicine team because of abnormal ultrasonographic findings at 34 weeks of gestation. The fetus has severe intrauterine growth restriction (IUGR) (<1st percentile) and multiple organ abnormalities, including microcephaly, small forebrain, scalloped parietal bones, bilateral ventriculomegaly, dilated third ventricle, splayed thalami, irregular falx, scattered intracranial calcifications, and a small, flattened forehead. Fetal echocardiography shows levorotation of the cardiac axis, tortuous ductus arteriosus, and tricuspid valve thickening.

Her prenatal history is notable for travel to the Dominican Republic until 12 weeks of gestation. She denies any fever, insect bites, rash, conjunctivitis, or arthralgia. Findings on other prenatal laboratory screening are reassuring.

After the induction of labor for IUGR, a male infant is delivered at 37 2/7 weeks of gestation via normal spontaneous vaginal delivery. Brief positive pressure ventilation is given in the delivery room for an initial low heart rate. The heart rate quickly recovers, but respiratory distress develops, requiring continuous positive airway pressure (CPAP). The infant is transferred to the NICU with the administration of CPAP.

Upon admission, physical examination shows a boy with a birthweight of 2,140 g (2.8th percentile), length of 40.5 cm (<1st percentile), and head circumference of 29 cm (<1st percentile). Pertinent findings include microcephaly and global hypertonia, along with contractures of the upper and lower extremities (Fig 1).

DISCUSSION

Symmetric IUGR often results from intrinsic fetal factors, with an extensive differential diagnosis that includes:

- Chromosomal abnormalities
- Congenital infections (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex, Zika virus [TORCH-Z])
- Inborn errors of metabolism

Chest radiography shows paralysis of the right hemi-diaphragm (Fig 2). Complete blood cell count, blood cultures, urine cytomegalovirus shell vial assay, and newborn screening for toxoplasmosis all had negative results. Given the extensive brain malformations, genetic and endocrine evaluations were performed. The karyotype was 46,XY. Cortisol, free thyroxine, luteinizing hormone,



Figure 1. Contractures of upper and lower extremities.

and follicle-stimulating hormone concentrations were all normal. A Zika virus diagnostic panel was sent and included:

- Maternal placenta for Zika virus RNA
- Maternal urine and serum Zika virus RNA
- Infant's blood for Zika virus immunoglobulin M (IgM) with confirmatory plaque reduction neutralizing antibody test (PRNT)
- Infant's urine and serum Zika virus RNA

Postnatal echocardiography revealed no structural abnormalities in the infant. Ophthalmologic evaluation was within normal limits. He did not pass his hearing screen. Ultrasonography of the hip demonstrated developmental dysplasia.

Diagnosis and Further Progress

The infant was gradually weaned from CPAP to nasal cannula. A postnatal magnetic resonance imaging (MRI) scan (Fig 3) revealed microcephaly, pachygyria, partial

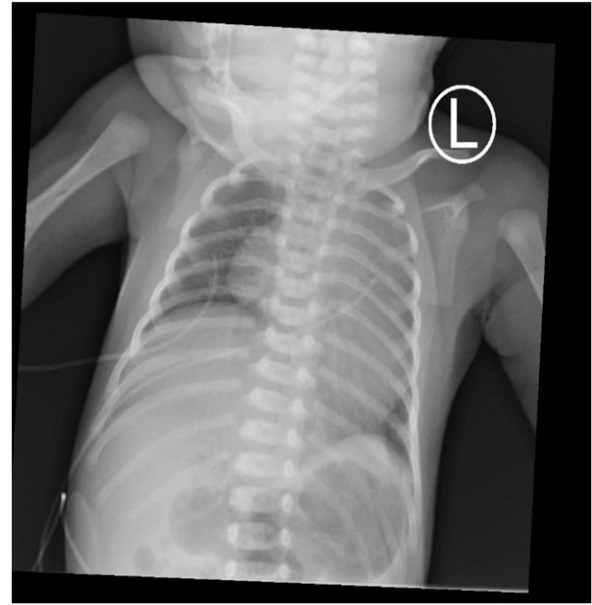


Figure 2. Chest radiograph showing right hemi-diaphragm paralysis.

agenesis of the corpus callosum, ventriculomegaly, vermian hypoplasia, and parenchymal calcifications. He was discharged from the hospital with full oral feeds and a nasal cannula.

Zika virus RNA returned positive for the placenta, but the mother's urine and serum samples were negative, as were the infant's urine and serum samples. Infant's Zika virus IgM was initially inconclusive, but the confirmatory PRNT result was positive for Zika virus and dengue. Based on the Centers for Disease Control and Prevention guidelines, the infant was considered presumptive positive for congenital Zika virus syndrome.

Audiology follow-up revealed moderate to severe hearing loss necessitating hearing aids. Ankle contractures and hypertonia required serial casting. He was seen by a pulmonologist who managed his nasal cannula support, with a plan to perform ultrasonography to further evaluate the hemi-diaphragm paralysis.

The Condition

The prenatal ultrasonographic findings, travel history, postnatal MRI, and positive Zika virus PRNT result are consistent with congenital Zika virus syndrome. Zika virus infection is a new teratogenic disease caused by the mosquito-borne flavivirus. Our knowledge of the congenital Zika virus syndrome is still evolving. (1) Zika virus causes direct cellular injury to the central nervous system with the live virus identified in brain tissues of

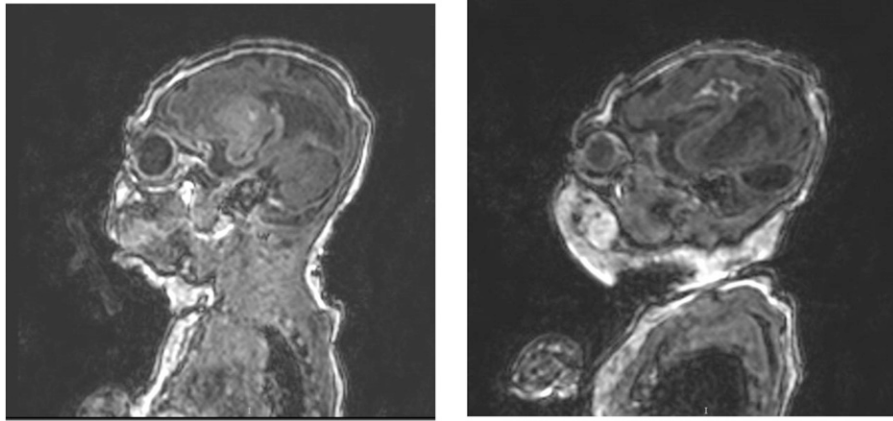


Figure 3. Postnatal magnetic resonance imaging scan showing microcephaly, pachygyria, partial agenesis of the corpus callosum, ventriculomegaly, vermian hypoplasia, and parenchymal calcifications.

affected infants. The primary target of the Zika virus is the neural progenitor cells, with immature neurons affected to a lesser extent. (2)

Symptoms such as fever, headache, arthralgia, myalgia, conjunctivitis, and maculopapular rash are suggestive of maternal infection with Zika virus. Risk of birth defects is highest if the infection is reported in the first trimester of pregnancy. (3)(4) Studies conducted in newborns with microcephaly due to Zika infection revealed a characteristic neuroimaging pattern that is distinct from other TORCH infections. (5) Fetal brain disruption sequence (severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and neurologic impairment), and brain anomalies (subcortical intracranial calcifications, severe cortical malformations, ventriculomegaly, agenesis of the corpus callosum, severe damage to the cerebellum, brain stem, and thalami), are characteristic and highly suggestive of congenital Zika virus infection. (2)(6) Ocular abnormalities associated with this entity include cataracts, coloboma, chorioretinal atrophy, focal pigment mottling of the retina, optic nerve hypoplasia, and atrophy. (2)(5) Extracranial abnormalities in congenital Zika virus syndrome include talipes, arthrogryposis, hyperflexion of the fingers, and diaphragm palsy. (2)(7)

Prenatal ultrasonography performed in the first trimester and early part of the second trimester (before 21 weeks' gestation) often yields false-negative results by detecting no abnormalities. (4) In addition, current laboratory testing for Zika virus has its limitations. Because of the delayed development, subsequent waning of Zika virus IgM, and the transient presence of the viral RNA in pregnancy, these tests may have negative results. (6)

Physicians should be aware of Zika virus endemic regions and consider evaluating for congenital Zika virus infection in infants who have clinical signs suggestive of congenital Zika virus syndrome. Maternal risk factors such as travel history to endemic areas or sexual contact with a person who traveled to such an area should be considered. Also at high risk are infants whose mothers have laboratory evidence suggestive of Zika virus infection during pregnancy. (6)

Postnatal Management

Congenital Zika virus infection is multisystemic. Multidisciplinary management includes neurology, ophthalmology, otolaryngology, orthopedic surgery, cardiology, endocrinology, genetics, and infectious diseases as indicated. Upon discharge, close supervision by a pediatrician and multidisciplinary follow-up is essential. (6)

Lessons for the Clinician

- A normal first- and second-trimester ultrasonography scan is not necessarily reassuring in cases of suspected congenital Zika virus infection. Adequate investigations and follow-up are essential in mothers at high risk for Zika infection.
- In the absence of maternal use of teratogens and negative laboratory results for other congenital infections, specific neuroimaging findings described herein are highly suggestive of congenital Zika virus syndrome.
- Zika virus syndrome should be considered in the differential diagnosis of an infant with microcephaly and multiple brain malformations.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of other maternal infections (eg, malaria) and their management.
- Know the causes, diagnosis, management, and outcome of an infant with microcephaly.

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ANSWER KEY FOR OCTOBER 2018 NEOREVIEWS

Diagnosing and Managing Hirschsprung Disease in the Newborn: 1. D; 2. E; 3. C; 4. B; 5. B.
Radiologic Approach to the Diagnosis of Bowel Emergencies in Neonates: 1. B; 2. E; 3. A; 4. B; 5. C.

Index of Suspicion in the Nursery

1 A Well-Growing Neonate with Features of Intestinal Obstruction

Ashish Jain, MD, DM,* Madhavi Bharadwaj, MD,* Siddharth Ramji, MD,*
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AUTHOR DISCLOSURE Drs Jain, Bharadwaj, and Ramji and Mr Agarwal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

CASE PRESENTATION

A 1,555-g, first of twin female infants is born at 38 4/7 weeks to a 24-year-old primigravida in a vaginal delivery through clear amniotic fluid. The infant is small for gestational age (<10th percentile on the Fenton intrauterine growth chart) with features of intrauterine malnutrition, such as triangular facies and loose skinfolds. The antenatal period is uneventful. The infant needs only basic steps at birth, with Apgar scores of 9, 9, and 9 at 1, 5, and 10 minutes, respectively. In view of the low birthweight, the neonate is transferred to the NICU and placed under the warmer with servo skin mode. Full tube feeding is initiated under observation.

The infant passes meconium on the first postnatal day at 18 hours of age and has a normal stool transition. She tolerates feeds well until day 6 after birth, with an expected weight loss of 1.2% per day. On the sixth postnatal day, she has abdominal distention (an increase in girth of 3 cm) with multiple episodes of vomiting. On evaluation, she is found to be eutermic (temperature of 98.9°F [37.2°C]), euglycemic (glucose concentration of 64 mg/dL [3.5 mmol/L]), normocalcemic (calcium concentration of 4.04 mg/dL [1.01 mmol/L]), with no evidence of any systemic illness. Hence, surgical causes like volvulus, Hirschsprung disease, meconium ileus, and acute/subacute intestinal obstruction are the most likely considerations in the differential diagnosis. A sepsis evaluation is nonsuggestive (total leukocyte count 7,600/ μ L [7.6×10^9 /L]; absolute neutrophil count 3,400/ μ L [3.4×10^9 /L]; micro-erythrocyte sedimentation rate 10 mm/h; immature to total neutrophil ratio 0.16). The abdominal radiograph is suggestive of gaseous distention with no air fluid levels (Figs 1 and 2).

In view of the persistent signs, despite normal findings, feeding is withheld and intravenous fluids are started, with continuous nasogastric aspiration with a 6F feeding tube. The rectal stimulation results in no improvement. On postnatal day 8, under strict asepsis, a glycerin saline enema (20 mL glycerin with 20 mL saline) is administered to the neonate under the supervision of the pediatric surgeon. The enema results in passage of greenish-yellow, pasty, putty, long stool plugs (Fig 3). Subsequently, the obstruction is relieved, and a normal stooling pattern observed. Feeding is resumed and a consistent weight gain with breastfeeding is noted in the following week. The infant is discharged on the 13th postnatal day. A follow-up at 14 weeks reveals normal growth and development with no complaints.

CASE DISCUSSION

After a thorough literature search, a diagnosis of inspissated milk syndrome with no recurrence was strongly considered in this case.



Figure 1. Abdominal radiograph of a supine infant showing gas-filled abdomen with nonsignificant findings.

The Condition

Inspissated milk syndrome is also known as *lactobezoar*, *milk bolus syndrome*, or *milk curd syndrome*, and has been reported in both the Indian and western literature. (1)(2) The best proposed etiopathogenesis of this condition is



Figure 2. Abdominal radiograph of an upright infant showing gas-filled abdomen with absence of fluid air levels.



Figure 3. Photograph of a long, inspissated stool, which is passed as greenish yellow, pasty, long stool plugs.

differential absorption of water and solid nonfats in the milk, leading to precipitation with mucous in the gastrointestinal tract. Several host and environmental factors have been proposed as predisposing newborns to this condition. Some of the most important factors are prematurity, low birthweight, overconcentrated formula (calorie content of >80 kcal/kg), high casein content ($>60\%$), high calcium content, use of special preterm formulas, and use of breast milk fortifiers. (1)(3) In the current case, the inspissation developed in a term and exclusively breastfed neonate. Hence, even though formula feeding and prematurity are reported to be associated and predisposing infants to milk bolus syndrome, they may not represent the primary pathology involved. Most infants present within 2 to 10 days after birth with features suggestive of acute obstruction, such as abdominal distention, vomiting, and gastric residues, as seen in the current case. The condition is seldom reported to present with abdominal mass.

Diagnosis

In most cases, radiology is nonspecific and does not help in the diagnosis. Various radiologic findings reported include absent gas shadow in right lower quadrant and air fluid levels in the small bowel, as seen in obstruction. Occasionally, specific findings like gastric mass with an air halo around it or fecal mass in the lower gut with a bubbly appearance and air trapped within have also been reported. Abdominal ultrasonography may show a free-floating intragastric mass or intrabezoaric echogenic foci suggestive of trapped air. In cases of lactobezoar located in the stomach (*gastric lactobezoars*), radiography may offer a specific clue because it is seen as a moving mass with a change in the patient's posture. (3) A sincere effort should always be made to rule out more sinister and common causes of acute intestinal obstruction like volvulus, intussusception, Hirschsprung disease, and meconium ileus.

After ruling out the common causes, a high index of suspicion in an “apparently well infant with features of acute intestinal obstruction” is essential to diagnose inspissated milk syndrome.

Treatment

Most cases of inspissated milk syndrome respond to conservative management. This includes gut rest, intravenous fluids, and gastric decompression. Gastrografin or N-acetyl cysteine gastric lavage, gastroscopic disintegration, and removal have also been used with variable success in gastric lactobezoars. (2)(3) Enema can be useful in cases with inspissation involving the lower part of the gut as in the current case. Occasionally, changes in milk formula alone have resulted in rapid improvement. The success of conservative treatment clearly argues against primary invasive measures. However, caution is warranted when the cause of acute abdomen remains elusive for more than 24 hours.

Rarely, in complications like perforation and when conservative management fails, surgical intervention is required.

Most of these infants are well, with an uneventful follow-up after the acute episode is relieved. One case of recurrence has been reported in a 30-week-old preterm neonate with tracheoesophageal fistula, who was started on formula feeding postoperatively; however, that infant was later diagnosed as having celiac disease. (4)

Lessons for the Clinician

- The diagnosis of inspissated milk syndrome requires a high index of suspicion in a relatively well infant suspected to have acute intestinal obstruction.
- Although this condition can occur in any infant, it is more common in preterm infants receiving high-calorie and/or fortified formula.
- The condition is usually managed conservatively, resulting in rapid resolution and a very good prognosis.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the factors that may inhibit or improve intestinal motility.

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Case 1: A Well-Growing Neonate with Features of Intestinal Obstruction

Ashish Jain, Madhavi Bharadwaj, Siddharth Ramji and Satish Agarwal

NeoReviews 2018;19:e42

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Index of Suspicion in the Nursery

3 Abdominal Distention and Bloody Stools in a 2-week-old Term Neonate

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PRESENTATION

A 2-week-old female neonate is born via cesarean section at 39 2/7 weeks to a 34-year-old gravida 3, para 2 woman with adequate prenatal care and negative serologic findings. During pregnancy, the mother develops gestational diabetes that was both diet and insulin controlled. The infant is exclusively breastfeeding at home.

At 17 days of age, the infant is brought to the emergency department (ED) with acute onset of bloody stools that occurred once, along with lime-yellow vomitus concerning for bilious emesis. The mother reports that the infant had been fussy the previous day with increased vomiting and nasal mucous discharge requiring bulb suction. She calls the pediatrician who recommends obtaining a rectal temperature, which is 98.6°F (37°C). Two hours later, the infant develops the rectal bleeding episode (Fig 1) and is brought to the ED at our institution.

In the ED, the physical examination findings are significant for increased fussiness on abdominal palpation, moderately distended firm abdomen, increased tympany, absence of bowel sounds, bright red blood in the diaper, and no anal fissures. Admission vital signs include a temperature of 99.3°F (37.4°C), heart rate of 152 beats/min, respiratory rate of 48 breaths/min, and oxygen saturation of 100% in room air. Complete blood cell count in the ED shows no evidence of leukocytosis, bandemia, or eosinophilia (white blood cell count of $16,000/\mu\text{L}$ [$16 \times 10^9/\text{L}$] with 1 band, platelets of $477 \times 10^3/\mu\text{L}$ [$477 \times 10^9/\text{L}$]). Coagulation profile is within normal limits (prothrombin time 12.6 seconds, partial thromboplastin time 28 seconds, international normalized ratio 1.0). Abdominal radiography in the ED shows “abnormal dilated bowel, without free air or pneumatosis. Ileus, necrotizing enterocolitis (NEC), and enteritis should be considered. The appearance is less consistent with malrotation; however, upper gastrointestinal (GI) endoscopy is recommended as clinically indicated” (Fig 2). Upper GI endoscopy is performed, which reveals no evidence of malrotation with persistent dilated distal bowel (Fig 3).

The infant is admitted to the pediatrics department and a surgery consultation is requested. Abdominal ultrasonography (AUS) reveals no evidence of pneumatosis with dilated bowel loops filled with liquid stools and moderate to large ascites with low-level internal echoes (Fig 4). The patient is given nothing by mouth, with a Replogle tube used for low intermittent suction and the infant is started on intravenous fluids. Being concerned about this unusual presentation in a term neonate, the NICU team decides to transfer her to their service. A sepsis evaluation is conducted and stool cultures are sent for bacterial as well as viral infections. Full AUS is performed to rule out ovarian cyst or ruptured ureterocele.

AUTHOR DISCLOSURE Ms McClelland and Dr Ibrahim have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Bright red blood in the diaper of the patient.

The AUS reveals normal liver, kidneys, and ovaries. Follow-up abdominal radiography shows persistent dilated bowel loops with no transition point. A barium enema is ordered after clearing of the upper GI contrast and shows normal colon with possible small bowel obstruction in the jejunum or ileum, which was ruled out on further abdominal radiography (Fig 5). On further clarification, the mother reports that the sibling was sick 2 weeks ago with upper respiratory tract symptoms. A respiratory viral panel is sent and is positive for rhino/enterovirus infection.

DISCUSSION

Hematochezia is the passage of gross blood per rectum. Factors necessary in assessing a child with hematochezia include age of the patient, color of the blood, presence of

abdominal pain/tenderness, and history of altered bowel movements. In 10% to 15% of mucosal or variceal hemorrhages from the upper GI tract, presentation can be melena without hematochezia. (1) Melena or dark blood usually originates from the stomach, duodenum, small bowel, or colon proximal to the ligament of Treitz.

Hematochezia in a neonate can occur because of various causes, ranging from benign to life-threatening conditions. Examples of benign etiologies include swallowed maternal blood (during delivery or nipple cracks during nursing), anal fissures, and milk protein allergy. Examples of more serious conditions include bacterial or viral infections (herpes simplex virus, adenovirus) causing colitis, NEC, or GI malformations. (2)

Causes can be divided into different categories: 1) allergy (eg, milk protein); 2) intolerance; 3) exogenous source such as swallowed maternal blood; 4) gastrointestinal such as anal fissures, Hirschsprung disease with enterocolitis, malrotation with volvulus, intussusception, Meckel diverticulum; 5) vascular malformations (hemangioma, arteriovenous); 6) infections, either bacterial (group B *Streptococcus*, *Escherichia coli*) or viral (herpes virus or cytomegalovirus), and infectious colitis (salmonella, shigella, rotavirus, norovirus); 7) hematologic disorders such as thrombocytopenia, vitamin K deficiency, disseminated intravascular coagulopathy; and 8) hypoperfusion to the gut such as NEC or congenital heart disease. (2)

The clinical presentation of the neonate at the onset of bloody stools helps narrow the differential diagnosis. In an ill-appearing neonate with abdominal distention and tenderness, bowel ischemia, with a manifestation of intussusception,

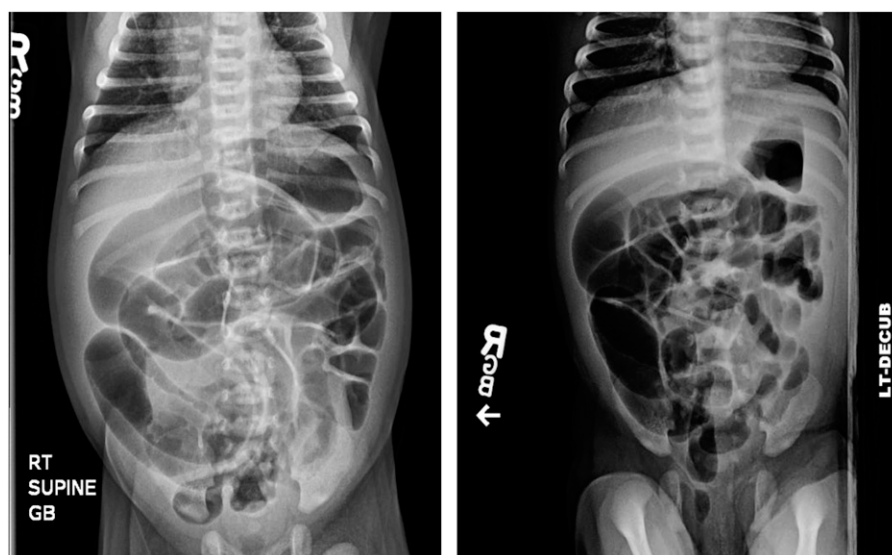


Figure 2. An anteroposterior view and left lateral decubitus of the patient showing abnormal dilated bowel with no free air or pneumatosis.



Figure 3. An upper gastrointestinal series of the patient showing no evidence of malrotation with persistent dilated distal bowel loops.

midgut volvulus, or mesenteric thrombosis, can be the cause. In children younger than 2 years, idiopathic intussusception can present with sudden onset of abdominal pain/tenderness and vomiting, followed by the passage of red currant jelly stools; these signs can be preceded by a viral infection in younger newborns versus a leading point such as Meckel diverticulum or polyp or nodular lymphoid hyperplasia in older children.

Painless hematochezia can be the result of Meckel diverticulum (occurring at <2 years of age in 50% of cases), polyp or intestinal duplication, malformation or superior mesenteric artery aneurysm.

One of the most serious causes of morbidity with bloody stools per rectum in a newborn is NEC, though it is uncommon in term neonates (1 in 20,000). (3) It presents clinically with emesis, abdominal distention, and radiographic findings of pneumatosis intestinalis, portal venous gas, or pneumoperitoneum. An alternative imaging modality that can aid in confirming the diagnosis is ultrasonography. Findings on

ultrasonography include portal venous gas, pneumoperitoneum, increased wall thickness, absent perfusion, or free fluid in the abdomen.

Anal fissures typically present with blood on the outside of normal-appearing stools, with physical examination findings of a fissure in the perianal area, usually posteriorly. Malrotation with midgut volvulus can be responsible for 75% of cases in the first month. Typically, it presents with sudden onset of bilious emesis, increasing abdominal distention, and eventually bowel necrosis leading to shock. Radiographically it can present with a gasless abdomen or distended bowel loops.

Milk protein enterocolitis is another entity that can present early but typically between 1 month and 1 year of age.

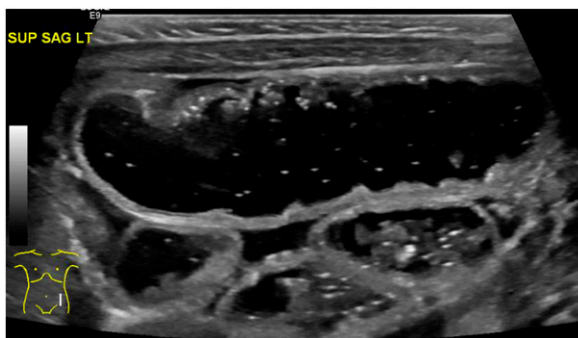


Figure 4. Dilated bowel loops with liquid stools on abdominal ultrasonography.



Figure 5. Barium enema showing normal colon.

About half of the patients are younger than 6 months. Symptoms related to the GI tract such as regurgitation, vomiting, colic, diarrhea, and bloody stools occur in 88.7% of the cases. (4) The most serious form of milk protein allergy in infants is protein-induced enterocolitis syndrome, which can present with vomiting, diarrhea, and a sepsislike picture.

Viral infections such as herpes or cytomegalovirus can lead to infectious colitis. In a rare case of congenital adenovirus infection, a 3-day-old infant presented with hematochezia and thrombocytopenia. (5)

In our case, the patient had a sibling with upper respiratory tract illness 2 weeks earlier. The patient tested positive for rhinovirus/enterovirus infection. The polymerase chain reaction assay in our laboratory cannot differentiate between both infections. We think that the patient might have developed viral colitis, which could have led to intermittent intussusception and presented with bloody stools. Another possibility is a severe form of cow milk protein allergy, but this is less likely given the lack of family history and the fact that the patient was only 2 weeks old.

FOLLOW-UP

The patient's abdominal symptoms improved, and the episodes of bloody stool ceased after 2 days of bowel rest. On consultation, the GI service recommended starting the patient on a special hypoallergenic infant formula to rule out severe milk protein allergy. The infant was discharged from the hospital after 5 days on full feeds with follow-up appointments scheduled with the pediatrician and the GI service.

Lessons for the Clinician

- Differential diagnosis of acute abdominal distention and bloody stools in a term neonate can be necrotizing enterocolitis, malrotation, or acute intestinal obstruction in an infant.
- However, despite being uncommon, severe milk protein allergy or a viral infection leading to colitis and/or intermittent intussusception can have a similar presentation.

- Acute abdominal distention and bright rectal bleeding can also occur because of a medical cause in some cases and might not need surgical intervention.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the laboratory and radiographic findings, evaluation, and management of GI bleeding in newborn infants
- Recognize the clinical signs, imaging features, and treatment of neonatal intussusception
- Know the clinical and diagnostic features, evaluation, management, and complications of NEC
- Know the differential diagnosis, diagnostic and laboratory features, and approach to management of infectious enteritis and colitis in the neonate
- Know the clinical manifestations, diagnosis, and management of allergic enteritis and colitis such as milk protein allergy
- Know the clinical manifestations and differential diagnosis of GI bleeding in newborn infants, including the various coagulation disorders that cause GI hemorrhage

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Case 3: Abdominal Distention and Bloody Stools in a 2-week-old Term Neonate

Katybeth McClelland and John Ibrahim

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Abdominal Distention and Gastrointestinal Bleeding in a Late Preterm Neonate

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AUTHOR DISCLOSURE Drs Raut, Badatya, Thakur, Kumar, and Kler have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A late preterm female neonate is born at 34 weeks, 6 days of gestation, with a birthweight of 2.1 kg. The mother is a gravida 2 woman and the infant is delivered via cesarean section in view of scar dehiscence. The infant cries immediately after birth and does not require any resuscitation. She develops respiratory distress in the delivery room, is transferred to the NICU, and given continuous positive airway pressure (CPAP). She is comfortable with CPAP and is gradually weaned to room air 48 hours after birth. On the third day after birth, tube feeding is commenced at 20 mL/kg per day. However, the next day she develops abdominal distention, gastrointestinal bleeding, and melena for which feeding is stopped. There is no history of treatment with steroids or nonsteroidal anti-inflammatory drugs. On the same day, she is transferred to a level IIIB NICU for further management.

On admission to the institute, the infant is lethargic and tachypneic. Blood pressure and capillary refilling time are in the normal range. The abdomen is soft without any distention and bowel sounds are present. There is no fresh gastrointestinal bleeding or melena. CPAP (positive end-expiratory pressure, -5 ; fraction of inspired oxygen, 21%) is restarted for respiratory distress.

CASE PROGRESSION

The infant is given nothing by mouth (*nil per os*; NPO) and total parenteral nutrition. Empirical antibiotic treatment (intravenous meropenem) is started after performing sepsis screening; laboratory testing for platelet count, prothrombin time, and activated partial thromboplastin time; and cultures of blood, cerebrospinal fluid, and urine. Arterial blood gas shows a pH of 7.21, bicarbonate of 14.4 mEq/L (14.4 mmol/L), and anion gap of 22, suggesting increased anion gap metabolic acidosis. Radiograph of the chest is normal but that of the abdomen suggests the presence of gas in the wall of the stomach (Fig 1). The total leukocyte count is $3,800/\mu\text{L}$ ($3.8 \times 10^9/\text{L}$), C-reactive protein is 68.5 mg/L (652.4 nmol/L), and prothrombin time, activated partial thromboplastin time, and platelet counts are in the normal range. Blood culture yields gram-negative bacteria, *Achromobacter xylosoxidans*, for which modified antibiotics are administered. The opinion of pediatric surgery is obtained, and the treating team and radiologist agree to treat her for isolated gastric pneumatosis without any bowel involvement. She is weaned to room air 36 hours after admission. Repeat radiography performed on days 7 and 10 after admission shows the resolution of pneumatosis (Figs 2 and 3). The infant continues to remain NPO for 10 days and starts receiving small

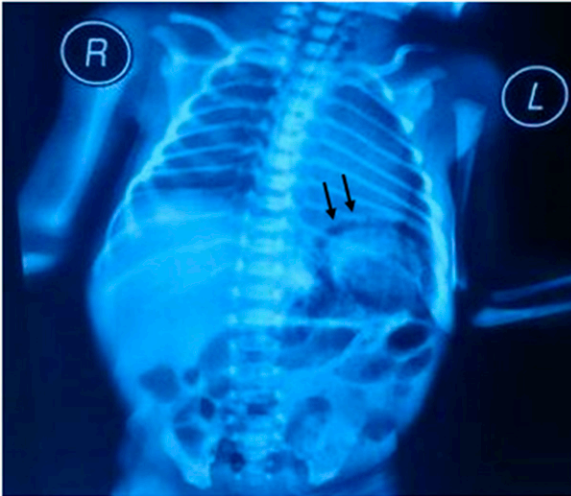


Figure 1. Radiograph of the abdomen on day of admission showing isolated gastric pneumatosis (black arrows).

feedings of 20 mL/kg per day on day 11 of admission. Feedings are gradually increased and she reaches a full feed of 150 mL/kg per day on day 18. For gram-negative bacterial sepsis, she is treated with antibiotics for 14 days and discharged 20 days after birth.

DISCUSSION

Isolated gastric pneumatosis in a neonate is very rare and only a few cases have been reported. Pneumatosis is defined

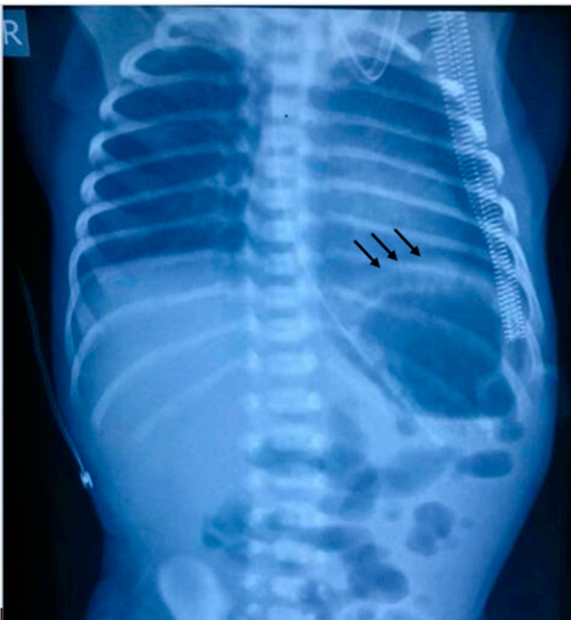


Figure 2. Radiograph of the abdomen on day 7 of admission showing partial resolution of gastric pneumatosis (black arrows).

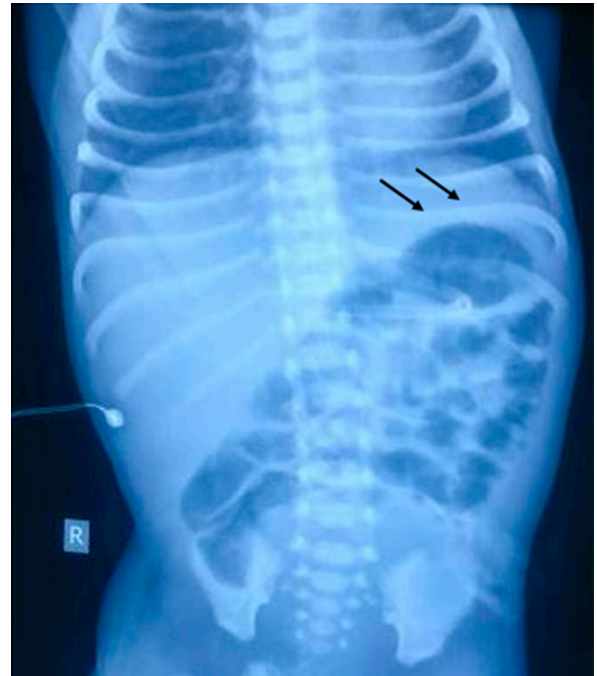


Figure 3. Radiograph of the abdomen on day 10 of admission showing complete resolution of gastric pneumatosis (black arrows).

as the presence of gas in the bowel wall. (1) However, it can involve any part of the gastrointestinal tract. Most cases of gastric pneumatosis are caused by obstruction of the proximal bowel because of pyloric stenosis, pyloric atresia, or duodenal web. (2)(3)

Gastric pneumatosis is of 2 types—gastric emphysema or emphysematous gastritis. Whenever intraluminal pressure is increased because of proximal bowel obstruction, the intraluminal gas dissects through the intact gastric mucosa and produces linear or cystic pneumatosis. (4) This is known as *gastric emphysema*. It has a good prognosis and these patients improve quickly once the obstruction is relieved. (5) Emphysematous gastritis has a more indolent course because of an infection or inflammation that causes a breach in the gastric mucosa, which is followed by gas entering the mucosa. It has a poorer prognosis and these patients usually take longer to recover. Management is usually conservative with the treatment of underlying infection/inflammation, but surgical exploration may be needed in the presence of pneumoperitoneum or suspicion of gangrene. (6) In the current case, there was no proximal bowel obstruction. Presence of gastrointestinal bleeding, metabolic acidosis, classic radiographic findings, normal coagulation profile, and positive blood culture favors the diagnosis of isolated gastric pneumatosis, with late prematurity and sepsis being the predisposing factors.

Lessons for the Clinician

- Usually gastric pneumatosis is associated with fulminant necrotizing enterocolitis or benign etiologies like upper gastrointestinal obstruction or drug exposure.
- Uncommonly gastric pneumatosis can occur in isolation and can present early, with prematurity and sepsis being the predisposing factors.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations and differential diagnosis of gastrointestinal (GI) bleeding in newborn infants, including the various coagulation disorders that cause GI hemorrhage.

- Know the laboratory and radiographic findings and management of GI bleeding in newborn infants.

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Abdominal Distention in a Term Infant with Unilateral Ventriculomegaly

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PRESENTATION

An early term female neonate is born at 37 weeks, 2 days of gestation with a birthweight of 3.1 kg. She is delivered vaginally by a 26-year-old woman after induction of labor for preeclampsia with severe features; magnesium sulfate was given during labor. Prenatal history is significant for late prenatal care (14 weeks) and fetal diagnosis of right-sided ventriculomegaly noted on serial ultrasonography, first at 20 weeks of gestation and confirmed on fetal magnetic resonance imaging (MRI) at 27 weeks. All prenatal serologic findings were negative, a 1-hour oral glucose tolerance test result was within normal limits, and cell-free fetal DNA was negative for trisomies 13, 18, and 21. Maternal-fetal medicine, neonatal-perinatal medicine, and pediatric neurosurgical physician teams were involved in the prenatal care, and a plan was developed to admit the infant to the level III NICU after birth for further brain imaging.

At delivery, the infant is vigorous, with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. Birthweight is at the 50th percentile, length is greater than the 97th percentile, and occipitofrontal circumference is at the 90th percentile. The remainder of the newborn examination is unremarkable, including a perforate anus, and the infant is admitted to the NICU for known right-sided ventriculomegaly. On the day of birth, postnatal MRI demonstrates asymmetric right-sided ventriculomegaly likely secondary to a prior germinal matrix and intraventricular hemorrhage. The infant feeds orally and voids normally but no stools are noted. At birth, a chromosomal microarray is obtained, which later reveals a likely benign duplication at 7q21.12-7q21.13, with no known clinical significance associated.

On the day after birth, the infant develops abdominal distention with decreased bowel sounds and lethargy. Oral feeding is discontinued and intravenous fluids are initiated. Vital signs are stable and examination findings are otherwise unremarkable, with no respiratory distress noted in room air. Voiding remains normal, but again, no stools are noted.

CASE PROGRESSION

A kidney, ureter, bladder (KUB) radiograph was obtained, which demonstrated mildly dilated loops of bowel throughout the abdomen. The infant was given nothing by mouth, and a Replogle tube was placed for abdominal decompression. Intravenous antibiotics (ampicillin and gentamicin) were started after performing a sepsis screen. The complete blood cell count and C-reactive protein levels were unremarkable. A repeat KUB radiograph remained concerning for a small bowel

AUTHOR DISCLOSURES Drs Lyle and Byrne have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

obstruction (Fig 1), and the infant developed bilious output from the appropriately positioned Replogle tube. A water-soluble contrast enema was performed on the third day, which revealed multiple intraluminal filling defects and meconium plugging (Fig 2). Shortly after the contrast enema, the infant began to pass stools, with 5 large-volume meconium stools noted in the following 24 hours. Abdominal distention and gastric output decreased, and a repeat KUB radiograph demonstrated decreased gaseous distention. Oral feedings were reinitiated 2 days after the enema and were advanced without difficulty. Daily occipitofrontal circumference measurements remained stable throughout the infant's hospitalization. She was discharged from the hospital on the 7th day after birth, voiding and stooling appropriately, and with follow-up scheduled with the neurosurgical team to continue to monitor the stable ventriculomegaly.

DISCUSSION

The differential diagnosis of abdominal distention in a newborn includes volvulus (with or without malrotation), necrotizing enterocolitis, sepsis, Hirschsprung disease, meconium syndromes (such as ileus or plug), intestinal webs or atresias, hypertrophic pyloric stenosis, congenital microcolon, spontaneous intestinal perforation, imperforate anus, peritoneal bands, internal hernias, and rarely, lactobezoars. (1)(2) Small left colon syndrome, first described

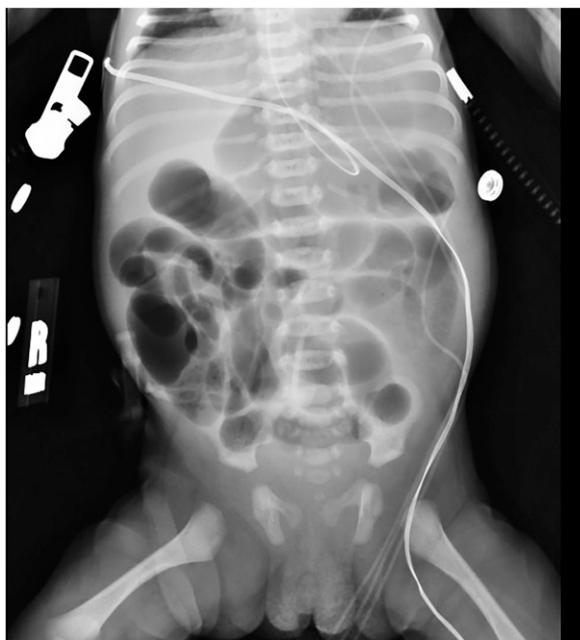


Figure 1. Small bowel obstruction noted on repeat kidney, ureter, bladder radiograph.



Figure 2. Multiple intraluminal filling defects and meconium plugging noted on water-soluble contrast enema.

in 1974, is thought to occur because of immaturity of the myenteric plexus ganglia (1) of the colon, which leads to a transient functional obstruction in newborns and carries a strong association with maternal diabetes mellitus, (3)(4) maternal preeclampsia treated with magnesium sulfate, (1) and prematurity. (1) Maternal diabetes mellitus, either gestational or pregestational, is the most common association, reported in 40% to 50% of the few published cases of small left colon syndrome. (3) Small left colon syndrome is the most common diagnosis in newborns who fail to pass meconium within the first 48 hours after birth. (1)(3)(4)(5)(6)

Abdominal radiography will demonstrate lower bowel obstruction with or without air-fluid levels. Water-soluble contrast enema is frequently both diagnostic and therapeutic in these patients, demonstrating a significant change in colonic caliber. An abrupt transition occurs at the splenic flexure to a narrow distal colon, relieving the obstruction by flushing away any meconium present in the distal colon. Normal intestinal motility without long-term complications is expected in cases of neonatal small left colon syndrome.

Lessons for the Clinician

- Delayed passage of meconium can be associated with disorders such as Hirschsprung disease; however, small left colon syndrome is the most common diagnosis.
- Small left colon syndrome carries a strong association with maternal diabetes mellitus.

- Any newborn who does not pass meconium within the first 48 hours after birth should have a prompt evaluation for obstruction, even if asymptomatic.
- Water-soluble contrast enemas are frequently both diagnostic and therapeutic in these patients.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Identify the developmental pattern for motility of various segments of the alimentary canal.
- Know the factors that may inhibit or improve intestinal motility.

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Case 2: Abdominal Distention in a Term Infant with Unilateral Ventriculomegaly

Allison N. J. Lyle and Bobbi J. Byrne

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Index of Suspicion in the Nursery

3

Abdominal Rash After Removal of Umbilical Vessel Catheter Anchor in a Preterm Infant

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AUTHOR DISCLOSURE Drs Ou, Kurtom, and Mitchell have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 635-g female infant is born at 25 weeks of gestation to a 36-year-old gravida 1, para 0 woman. The infant is twin B of a monochorionic-diamniotic twin gestation. The pregnancy is complicated by intrauterine growth restriction in twin A and polyhydramnios in twin B. The woman is a carrier for Gaucher disease and α_1 -antitrypsin deficiency and the family history is noncontributory. Prenatal screening for syphilis, human immunodeficiency virus, hepatitis B, hepatitis C, and *Toxoplasma* are negative and rubella immune. Group B *Streptococcus* status is unknown. Maternal history is negative for herpes simplex virus (HSV) and she denies having any lesions before or during pregnancy. The infants are born via emergency delivery because of the reversal of flow on umbilical arterial Doppler ultrasonography performed for twin A; rupture of membranes occurs at delivery. The infant's Apgar scores are 6 at 1 minute and 7 at 5 minutes. Vital signs are within normal limits, and physical examination findings at birth are unremarkable. On admission to the NICU, she develops severe respiratory distress necessitating intubation, surfactant administration, and synchronized intermittent mandatory ventilation. An umbilical venous catheter is placed and reinforced with an umbilical vessel catheter anchor. A blood specimen is obtained for culture and empirical antibiotic given for respiratory distress. On postnatal day 2, she is switched to high-frequency oscillatory ventilation because she is hypercapnic. Echocardiography reveals a large patent ductus arteriosus with bidirectional shunting, which subsequently closes on postnatal day 5 after 5 doses of ibuprofen. On postnatal day 7, the umbilical venous catheter and anchor are removed and the skin to the right of the umbilicus abraded. On postnatal day 14, the medical team notices new pustular and vesicular lesions (Fig) on her abdomen over the same area. Further laboratory investigations confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the current patient's vesiculobullous rash includes bullous impetigo, group A and group B streptococcal infection, fungal infection, congenital syphilis, congenital varicella syndrome, and HSV infection. Impetigo appears pustular or as erythematous papules that later develop honey-colored crusting and is often seen in areas of previous trauma, as could have occurred after removal of the umbilical vessel catheter anchor. Although rare, group B

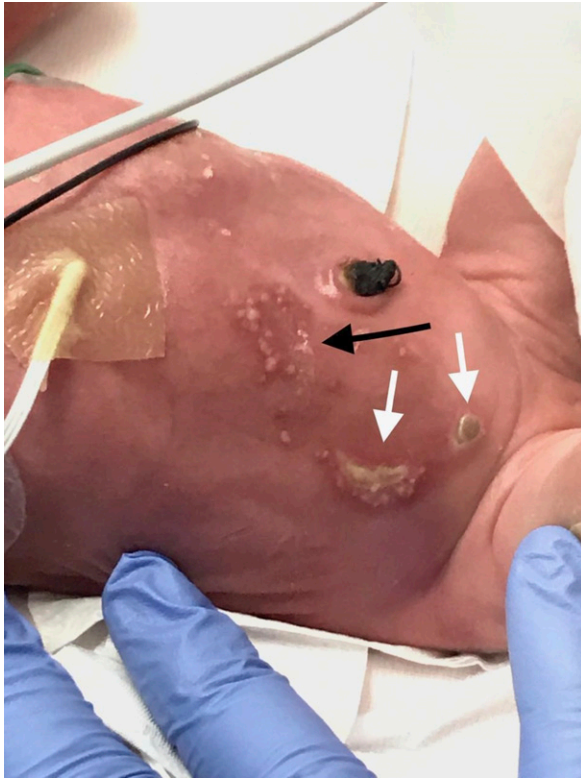


Figure. Pustular (white arrows) and vesicular (black arrow) lesions on the right side of the abdomen.

streptococcal infections can cause a bullous rash as well. *Candida* infections are the most common type of fungal infection and can cause erythematous lesions with discrete or confluent erythematous papules and plaques. The skin lesions in congenital syphilis can be seen at birth or present within 4 to 8 weeks after birth and typically involve the hands and soles. (1) One percent to 2% of infants born to mothers with varicella infection acquired between 8 and 20 weeks of pregnancy will have congenital varicella syndrome, which is characterized by vesicular lesions and cicatricial scarring, chorioretinitis, microphthalmos, nystagmus, limb hypoplasia, and central nervous system (CNS) damage when it does not cause death. (2)

Congenital cytomegalovirus presents in 1% of newborns and is the most common congenital viral infection in the United States. (1) Although most infants are asymptomatic, 10% of patients develop symptoms such as jaundice, hepatosplenomegaly, microcephaly, seizures, and sensorineural hearing loss. Skin manifestations are characteristically petechial and purpuric in nature, unlike the vesicles seen in our patient, and typically appear with other symptoms, rather than in isolation. (3)(4)

In our patient, the vesiculobullous lesions appear most consistent with HSV lesions, potentially precipitated by

the skin breakdown caused by removal of the umbilical vessel catheter anchor. Prenatal screening for toxoplasmosis, other agents, rubella (also known as German measles), cytomegalovirus, and herpes simplex (TORCH) syndrome reveals patients to be HSV-1 immunoglobulin (Ig)G positive, HSV-2 IgG negative, HSV-1/2 IgM positive. These immunoglobulin concentrations are not conclusive for the diagnosis or timing of maternal disease; HSV polymerase chain reaction (PCR) had not been performed on the mother prenatally. In addition to viral cultures from the patient's skin lesions, surface viral cultures from the eyes, nasopharynx, and rectum are sent and are negative. A blood PCR for HSV, cerebrospinal fluid (CSF) specimen for cells, chemistries, Gram stain, and aerobic culture are also obtained and found to be negative. The Tzanck smear from the skin lesions is positive for multinucleated giant cells, which can be seen in herpes or varicella infections. Acyclovir and vancomycin treatment are started; vancomycin is discontinued when cultures remain negative for 2 days. She is treated with parenteral acyclovir 60 mg/kg per day for 21 days and oral suppressive acyclovir for 6 months, which has been shown to improve neurodevelopmental outcomes in CNS disease and prevent the reactivation of cutaneous manifestations. (5) CSF PCR for HSV is performed and found to be negative before the completion of parenteral therapy.

DISCUSSION

The incidence of neonatal herpes ranges between 1 in 3,000 and 1 in 20,000 live births. Neonatal herpes can manifest in 3 forms, with potential overlap between the categories: 1) disseminated disease, most commonly involving the liver and lungs, but also CNS—occurring in 20% of HSV cases; 2) localized CNS disease—30%; or 3) disease localized to the skin, eyes, and/or mouth (SEM disease)—45%. The best morbidity and mortality outcomes occur with SEM disease. Most infants with CNS disease survive but will have substantial neurologic consequences. Thirty percent of infants with disseminated disease and 6% of infants with CNS disease die even when treated appropriately with acyclovir. (1)

Understanding the potential risks and modes of HSV transmission may guide clinical judgment and increase the clinician's awareness of possible neonatal infection. Transmission most commonly occurs through contact with the maternal genital tract; however, it can also occur via ascending infection through ruptured or even intact amniotic membranes. Rarely, intrauterine infections can cause congenital malformations, and postnatal transmission from a

parent or caregiver, likely from the hands or mouth, can occur. (6) Using cesarean delivery as the method of delivery decreases the risk of transmission through genital contact, but given the other potential modes of transmission, the clinician should not feel completely reassured that no transmission has occurred simply because of the cesarean delivery. One study found that the incidence of HSV infection in infants with mothers with HSV is 7.7% when delivered vaginally, and that although decreased, 1.2% of infants delivered via cesarean still develop an HSV infection. The risk of transmission is significantly higher in mothers who acquire HSV later in pregnancy compared with those who acquire HSV earlier in the pregnancy or before pregnancy. Because of the high efficiency of transmission of newly acquired HSV, 50% to 80% of neonatal HSV cases result from genital HSV acquired relatively soon after delivery, despite the fact that more infants are born to women with long-established HSV-2. (7) Although there is a correlation between the length of time from when an infection is acquired and the avidity of the infection and its efficiency of transmission, there are limitations to the practical application of this knowledge. First, it is difficult to determine the timing of maternal acquisition based on history or physical examination findings. As many as 75% of infants who acquire HSV infection are born to women with no history or physical examination findings suggestive of genital HSV infection. (1) These women are therefore unaware of their infection. Second, the physical examination findings of symptomatic women with HSV infections, such as vaginal discharge, genital pain, and shallow ulcers, are nonspecific and therefore difficult to diagnose. (8) Inquiries about the sexual partner's history of HSV can aid decision-making when the mother does not have any history or physical examination findings.

Maternal seropositivity is associated with decreased risk of transmission, because seronegativity corresponds to infants who lack transplacental antibodies and indicates primary HSV-1/2 infection and thereby a higher risk of transmission. In addition, the rate of transmission of HSV-1 appears to be higher than that of HSV-2. Previously, HSV-2 was the primary cause of genital infections, but currently, HSV-1 accounts for more than 50% of genital infections. Conversely, women with an HSV-2 infection before pregnancy are at a low risk of transmitting HSV-2; previous HSV-2 infection also has a protective effect against the transmission of HSV-1. Other risk factors for neonatal HSV include HSV isolation from the cervix, invasive monitoring (eg, scalp electrodes) with the potential to cause loss of skin integrity, and maternal age less than 21 years. (6)

Lessons for the Clinician

A high index of suspicion for HSV infection is important in symptomatic neonates. Unfortunately, the diagnosis can be complicated by many factors. Symptoms can present anytime in the first 6 weeks after birth; SEM and disseminated disease typically present in the first 1 to 2 weeks and localized CNS disease usually presents between the second and third weeks after birth. (1) In addition, manifestations are varied, and although they are categorized into 3 groups, the categories may have overlapping symptoms and can include respiratory distress, seizures, lethargy, shock, liver failure, or coagulopathy, with only two-thirds of those with disseminated or localized CNS disease also presenting with skin lesions. (1)

The diagnosis is further obscured in premature infants, as in the 25-week infant described here. Her nonspecific symptoms may be secondary to HSV infection, but could also be explained by the other morbidities that accompany prematurity, such as respiratory distress syndrome or patent ductus arteriosus. There are few studies that focus specifically on premature infants. One retrospective study with infants at a mean gestational age of 27 weeks found that premature infants tend to have more severe disease manifestations; they are more likely to have disseminated and CNS disease, rather than SEM disease. The immaturity of the innate immune system and lack of transplacentally acquired immunity could lead to more disseminated disease, because the maternal transfer of antibodies does not begin until 20 to 22 weeks' gestational age. The symptoms most commonly found in premature neonates are respiratory distress, hypotension/poor perfusion, and lethargy. (9)

In the present case, the mother did not have a history of HSV. Therefore, when vesicular and bullous lesions were noted on postnatal day 14, the differential diagnosis was broad but included HSV infection. With the maternal serologic findings in this case, IgG-positive, HSV-2 IgG-negative, HSV-1/2 IgM-positive HSV-1, we are not able to definitively determine whether the mother has a reactivated HSV-1 infection or a nonprimary first-episode HSV-2 infection. Because of the homology between HSV-1 and HSV-2 (50% shared base pairs), differentiating between HSV-1 and HSV-2 IgM is not possible with the test used. IgM is not recommended in screening, because the sensitivity is low (79% in one study). (10) In addition, the specificity of the serologic tests is lowered by cross-reactivity with the IgM of other viruses. In the test used by our laboratory, cross-reactivity has been reported with Epstein-Barr virus, cytomegalovirus, and *Toxoplasma* IgM. When

present in high levels, rheumatoid factor and antinuclear antibody can also interfere with the test.

Despite the nuances involved in interpreting the clinical significance of the serologic tests, these results heighten our suspicion for HSV SEM disease acquired during pregnancy, at birth, or after birth. An initially reassuring aspect of our patient's history was the cesarean delivery with rupture of membranes at the time of delivery, but transmission can still occur with an ascending infection without rupture of membranes. (6) As discussed before, the clinician's index of suspicion must remain high despite the cesarean delivery and negative maternal history, because neither factor definitively rules out HSV transmission.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.

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Case 3: Abdominal Rash After Removal of Umbilical Vessel Catheter Anchor in a Preterm Infant

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Index of Suspicion in the Nursery

2 Acute Respiratory Distress, Hypoxia, and Pulmonary Hypertension in the Nursery

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AUTHOR DISCLOSURE Drs Muise and Tran have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is born at 39 weeks' gestation to a 28-year-old, gravida 3, para 2 woman who received regular prenatal care. Her history is significant for blood type O negativity (for which she received Rho(D) immunoglobulin at 28 weeks), hypothyroidism (treated with levothyroxine), polycystic ovarian syndrome (treated with metformin), and anxiety. The neonate is born via repeat cesarean section with vacuum assistance. The infant's Apgar scores are 9 and 9 at 1 and 5 minutes, respectively.

In the well-child nursery, the infant is hypoxic and has an oxygen saturation of 40%, requiring nasal continuous positive airway pressure of 5 cm H₂O and fraction of inspired oxygen (FiO₂) of 50%; she is transferred to the NICU.

FURTHER DIAGNOSTIC EVALUATION

In the NICU, she was noted to have increased work of breathing, and required nasal intermittent mandatory ventilation and FiO₂ of 50%. Chest radiography suggested respiratory distress syndrome versus pneumonia. Blood and urine samples were obtained for culture, and she was started on empirical antibiotic treatment for clinical pneumonia in the setting of presumed sepsis. Pediatric cardiology was consulted because of the clinical suggestion of pulmonary hypertension. Hyperoxia test, electrocardiography, and echocardiography showed no evidence of congenital heart disease. An incidental finding of ductus arteriosus thrombus extending to the main pulmonary artery and left pulmonary artery was uncovered on echocardiography (Figs 1 and 2).

Hematology consultation led to a recommendation of a complete thrombophilia evaluation including protein C, protein S, antithrombin III, homocysteine, and antiphospholipid antibody panel, all of which were normal. The initial platelet count was 152,000/ μ L (152×10^9 /L), and there were no signs of consumptive coagulopathy. All laboratory values were within normal limits. The infant was given a bolus (75 U/kg) of unfractionated heparin and started on a high-dose heparin infusion (28 U/kg per hour); she subsequently made a transition to low-molecular-weight heparin after head ultrasonography demonstrated no intracranial hemorrhage.

Within the first week after birth, the infant was weaned off respiratory support and was stable in room air. Blood and urine cultures yielded no growth after 48 hours, and she completed a 7-day course of ampicillin and gentamicin for clinical pneumonia. She was also found to have ABO incompatibility; maternal blood

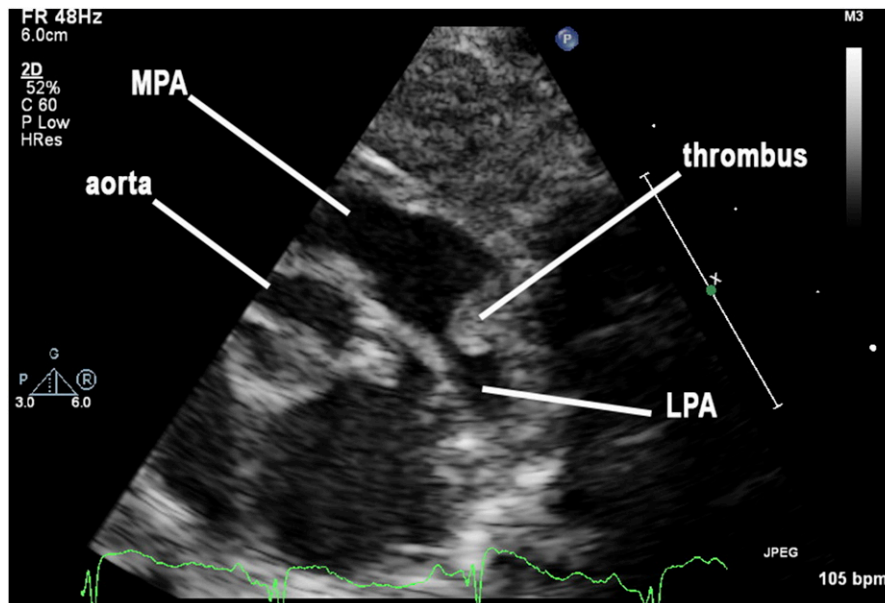


Figure 1. Echocardiographic parasternal short-axis view shows a cross-sectional image of the heart. Here the thrombus is protruding from the patent ductus arteriosus into the main pulmonary artery (MPA) and left pulmonary artery (LPA).

type was O negative, and the mother received Rho (D) immunoglobulin at 28 weeks' gestation; infant blood type was A positive with positive direct Coombs test result at birth, and the infant was treated with a 4-day course of phototherapy (her peak bilirubin level was 9.6 mg/dL [164.2 μ mol/L]). Thyroid levels, obtained at discharge because of maternal hypothyroidism with unknown etiology, were within normal limits for age.

At outpatient follow-up, the infant was asymptomatic and without respiratory distress or feeding difficulty. Follow-up echocardiography performed at 1 month of age demonstrated normal Doppler profile in right, left, and main pulmonary arteries with no evidence of thrombus. Anti-coagulation was stopped at 2 months of age, and repeat echocardiography identified no evidence of thrombus at 1 and 2 years of age.

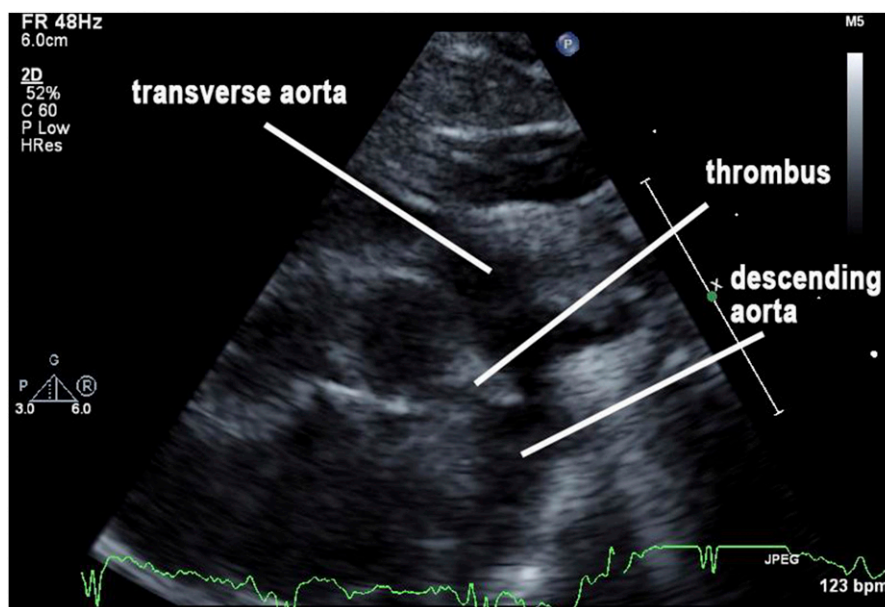


Figure 2. Echocardiographic images captured along the suprasternal notch view demonstrate the aortic arch. Here the patent ductus arteriosus thrombus is seen protruding into the descending aorta.

DISCUSSION

Thrombosis of the ductus arteriosus in the neonatal period is a rare finding, and has been historically associated with spontaneous ductus arteriosus aneurysm and with arterial access catheters. (1) Though typically asymptomatic, extension of ductus arteriosus thrombosis into other vessels or embolism can be life threatening, and may prompt surgical evaluation for possible thrombectomy and closure of the ductus. Medical management with either anticoagulation or antiplatelet therapy may also be considered in conjunction with or as an alternative to surgical correction.

At birth, the ductus arteriosus averages 15 mm in length and 4 mm in diameter. (2) It is derived from the embryologic portion of the left sixth aortic arch where it connects to the left main pulmonary artery, and is destined to become the ligamentum arteriosum. Physiologic closure of the ductus occurs in the hours to days after birth, and is a function of the contraction of the muscularis layer of the wall, causing infolding and buckling of the intima, beginning at the pulmonary artery end. Progression of physiologic closure leads to anatomic closure within several months. Thrombosis does not occur as a normal part of ductus arteriosus closure.

The incidence of ductus arteriosus aneurysm is low—1.5% detected on fetal echocardiography and 8.3% on postnatal echocardiography. (3) The theory most cited suggests that the aneurysm is formed by delayed closure of the aortic end of the ductus. (4) However, because some have been found as early as the third trimester, the mechanism of formation for prenatal compared with postnatal ductus arteriosus aneurysm may be different. The proposed mechanism for in utero aneurysm formation identifies higher flows through the ductus, suggesting that the aortic end is always open due to higher pressures. (4) Conical shape narrowing toward the pulmonary artery insertion creates a relative outflow obstruction across a ductus arteriosus aneurysm, and likely predisposes to thrombus formation. Serious complications of ductus arteriosus aneurysm are rupture, erosion, infection, and thromboembolism.

The neonatal period is a relative prothrombotic state, intensified by dehydration and acutely worsened in the settings of sepsis and trauma. Introduction of umbilical catheters also is associated with a predisposition to clot formation.

The Condition

Early reports of ductus arteriosus thrombosis largely described autopsy findings of dilated ductus arteriosus and thrombus. In 1972, Niwayama and Vadakan reported 13 historic cases and 3 new cases of thromboembolism due to anatomic anomalies (aneurysmal dilation, partial

thrombosis without embolization, and mycotic vegetations). (2) Knowlson and Marsden reported 3 new cases of systemic thrombi originating in the ductus arteriosus diagnosed at autopsy. (5) Morisot et al reported a case of neonatal hypertension resulting from renal artery embolism caused by ductus arteriosus thrombosis, which was successfully treated with thrombolytic therapy. (6) Thrombosis of the ductus arteriosus with extension of the clot into the pulmonary artery, as in this case, has previously been described; however, anticoagulation failed to prevent the propagation of the thrombus and the neonate required surgical thrombectomy. (7) Maisel and Brenner published a case of spontaneous closure of a ductus arteriosus thrombosis in the setting of a prenatally diagnosed ductal aneurysm. (8)

More recent case reports include systemic thromboembolism, causing acute cerebral infarct diagnosed with computed tomography angiography, with the incidental finding of ductus arteriosus aneurysm. (3)

Treatment

Treatment of thrombus originating in the ductus arteriosus varies with the severity of cardiopulmonary compromise. Observation, systemic anticoagulation, and surgical thrombectomy have all been described as treatment modalities for ductus arteriosus thrombus. The objective of treatment is to prevent both propagation of existing thrombus and development of new thrombosis. Surveillance with serial echocardiography is also recommended. (7) A full hypercoagulable evaluation may be performed regardless of treatment to uncover common causes of a thrombophilic state.

CONCLUSIONS

This case describes a potentially fatal ductus arteriosus thrombus that presented within the first hours after birth with pronounced hypoxia. Incidental echocardiographic finding of ductus arteriosus thrombosis extending into the main pulmonary artery and left pulmonary artery identified the likely source of pulmonary hypertension causing respiratory distress. Thrombosis prompted a negative hypercoagulability evaluation and led to successful treatment with systemic anticoagulation and subsequent clinical improvement.

Lessons for the Clinician

- A term neonate presenting with hypoxia within hours of birth requires a rapid assessment and consideration of a broad differential diagnosis, which may include transient tachypnea of the newborn, ductal-dependent cardiac lesions, hypoglycemia, and early-onset sepsis.

- With concurrent history and physical examination, emergent respiratory support to ensure adequate ventilation and oxygenation is essential.
- Early echocardiographic examination to evaluate for cardiac causes of hypoxia and timely intervention should be considered.

ACKNOWLEDGMENTS

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American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical features and differential diagnosis of persistent pulmonary hypertension.

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Index of Suspicion in the Nursery

3 Ambiguous Genitalia in a Newborn

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AUTHOR DISCLOSURE Drs Viehl, Gaut, Dandamudi, and Davis have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 3,250-g term infant is born via cesarean delivery to a gravida 1, para 0 woman at a community hospital. There are no complications during pregnancy. All maternal serologic test results are negative, including indirect Coombs, rubella, rapid plasma reagin, hepatitis B surface antigen, human immunodeficiency virus, *Gonorrhea*, *Chlamydia*, and group B *Streptococcus*. The infant is delivered via cesarean section because of a failure to progress during induction of labor. Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. Growth parameters for weight, length, and orbitofrontal circumference are within the expected range for gestational age. Physical examination is notable for ambiguous genitalia with an enlarged clitoris with prepuce, enlarged labia majora bilaterally, and small labia minora bilaterally. No testicles are palpated within the inguinal canal. The infant is transferred to the NICU.

Abdominal and pelvic ultrasonography reveals normal-appearing adrenal glands, a normal-appearing uterus, and an absence of intra-abdominal gonads. A congenital adrenal hyperplasia (CAH) panel reveals normal levels of androstenedione, cortisol, dehydroepiandrosterone serum, deoxycorticosterone, 17-hydroxypregnenolone, 17-hydroxyprogesterone, testosterone, and 11-deoxycortisol. It reveals a markedly elevated level of progesterone of 261 ng/dL (830 nmol/L; normal range for our laboratory is <10 ng/dL [32 nmol/L] for a patient of this age). Chromosome analysis using fluorescence in situ hybridization reveals a 46,XY karyotype and a normal chromosomal microarray. Antimüllerian hormone level is in the normal range for a genotypic male. The infant is discharged from the NICU with a recommendation to follow up with the endocrinologist.

The infant presents to the hospital at 4 months of age with concerns for several metabolic derangements, including serum sodium of 115 mEq/L (115 mmol/L), potassium of 6.9 mEq/L (6.9 mmol/L), bicarbonate of 14 mEq/L (14 mmol/L), urea nitrogen of 65 mg/dL (23 mmol/L), creatinine of 2.9 mg/dL (256 μ mol/L), and calcium of 7.0 mg/dL (1.75 mmol/L). Dipstick urinalysis shows pH 7.0, 3+ protein, 3+ blood, with trace leukocyte esterase and no nitrites. The urine has more than 600 mg/dL of protein and 38 mg/dL of creatinine. Kidney ultrasonography reveals large echogenic kidneys. The left kidney measures 7.64 cm (3.3 standard deviations above the mean) and the right kidney measures 7.34 cm (2.9 standard deviations above the mean). Further genetic testing and input from consulting services confirm the diagnosis.

DISCUSSION

Differential Diagnosis

An infant with virilization always raises concerns for CAH. An elevation of 17-hydroxyprogesterone would be suggestive of 21-hydroxylase deficiency, the most common cause of CAH. In the setting of the XY karyotype with the appearance of female external genitalia (enlarged clitoris and labia majora), undervirilization may be responsible. Forms of CAH that need to be considered are 17 α -hydroxylase and 3 β -hydroxysteroid dehydrogenase deficiencies as well as lipoid hyperplasia and P450 oxidoreductase deficiency. However, an isolated elevation in progesterone does not necessarily suggest any particular diagnosis, especially given recent gestation. Antimüllerian hormone in the normal range helps rule out the diagnosis of müllerian duct abnormalities. Other diagnostic possibilities in cases of ambiguous genitalia and/or differences/disorders of sexual development include androgen insensitivity, 5 α -reductase deficiency, Leydig cell hypoplasia, aromatase deficiency, Smith-Lemli-Opitz syndrome, and gonadal dysgenesis.

The concomitant kidney involvement (nephrotic range proteinuria and elevated serum creatinine) in a genotypic male with undervirilization is concerning for a genetic renal syndrome such as a diagnosis on the Denys-Drash syndrome (DDS)–Frasier syndrome spectrum, WAGR (Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability [formerly referred to as mental retardation]) syndrome, or other *WT1* mutations (Table). Next-generation sequencing was performed on this patient to evaluate 34 genes implicated in genetic causes of steroid-resistant nephrotic syndrome. Testing revealed a pathogenic heterozygous missense variant, p.H445R (also known as p.H377R), in exon 8 of *WT1*, supporting the diagnosis of DDS in this patient. (1)(2) No significant variants were identified in any of the 33 additional genes tested.

The Condition

DDS is a congenital/infantile nephrotic syndrome caused by genetic mutations on exons 8 and 9 of the *WT1* gene. Patients have a male karyotype (46,XY), gonadal dysgenesis (external genitalia are ambiguous or appear as completely female—also known as male pseudohermaphroditism), and nephrotic syndrome and/or kidney failure (usually within the first 3 years of life). There is a greater than 70% predisposition for the development of Wilms tumor. There is also a predisposition for developing gonadoblastoma in the dysmorphic (streaked) gonads.

DDS is an autosomal dominant disorder. However, most mutations occur de novo. All mutations, recorded to date, result in a premature stop codon. The *WT1* protein is a transcriptional regulator of genes necessary for normal kidney development and ongoing function. The gene consists of 10 exons, with exons 7 to 10 encoding 4 zinc finger transcription factors that regulate gene expression by DNA and RNA binding. (3)

Although DDS can present with focal segmental glomerulosclerosis on kidney biopsy, most often, it shows diffuse mesangial sclerosis (DMS) (Fig 1A). DMS is characterized by immature-appearing glomeruli with increased mesangial matrix and hyperplastic visceral epithelial cells. As the lesions progress, the glomerular tuft becomes more retracted with capillary loop obliteration and increasing mesangial matrix. DMS is not specific for DDS and also has been identified in patients with pathogenic genetic variants in *PLC1E* and *LAMB2*. (4) The risk for gonadoblastoma is almost exclusively in the XY karyotype, and occurs because of neoplastic transformation of germ cells of the dysgenetic gonads. The risk for gonadoblastoma in DDS is approximately 4%.

Clinical Management

The presentation of significant kidney dysfunction requiring emergent kidney replacement therapy, large echogenic kidneys, streaked gonads, and a pathogenic heterozygous missense variant, p.H445R in *WT1*, prompted us to recommend proceeding with prophylactic bilateral nephrectomy and gonadectomy. Pathologic examination of the kidneys reveals diffuse mesangial sclerosis and scattered intralobar nephrogenic rests (Figs 1A and 1B). Nephrogenic rests are precursors of Wilms tumor.

Gonads have pathology consistent with fallopian tubes, seminiferous tubules and epididymis. Within the seminiferous tubules there are abnormal foci of Sertoli cells consistent with pregonadoblastoma lesions. After healing from the intra-abdominal surgery, the infant was discharged from the hospital on peritoneal dialysis. The parents have decided to raise her as a girl. Performing prophylactic bilateral nephrectomies and gonadectomy before the development of Wilms tumor or gonadoblastoma will allow proceeding to kidney transplantation when medically stable.

Lessons for the Clinician

- Denys-Drash syndrome (DDS) presents with the triad of early-onset nephropathy, genotypic male with undervirilization, and predisposition to Wilms tumor.
- *WT1* mutations that cluster in exons 8 and 9 are responsible for DDS.

TABLE. Wilms Tumor 1 Gene Mutations and Associated Syndromes

SYNDROME/DISEASE ASSOCIATED WITH WT1 GENE MUTATION	SITE OF MUTATION IN THE WT1 GENE ON CHROMOSOME 11P13	CLINICAL PHENOTYPE	TUMOR RISK
Denys-Drash syndrome	Mutations at either exon 8 or 9	Karyotype 46,XY*: Undervirilization with ambiguous or normal-appearing external female genitalia Streaked gonads/gonadal dysgenesis (male pseudohermaphroditism) Infant-onset, steroid-resistant, nephrotic syndrome with progression to ESKD by 3 years of age	70%–90% risk of developing Wilms tumor; greater incidence of bilateral disease 4% gonadoblastoma
Frasier syndrome	Mutations in intron 9 altering the ratio of WT1 isoforms	Karyotype 46,XY: Complete undervirilization; normal-appearing external female genitalia Streaked gonads/gonadal dysgenesis; (male pseudohermaphroditism) Diagnosis often identified during evaluation for primary amenorrhea Late childhood/adolescent onset, steroid-resistant, nephrotic syndrome with progression to ESKD by 20 years of age	4% risk of developing Wilms tumor 40% risk of gonadoblastoma
WAGR syndrome	Large deletion of adjacent genes at the p13 chromosomal region including <i>PAX6</i> gene; <i>PAX6</i> is responsible for aniridia and intellectual impairment	Karyotype 46,XY or XX Aniridia Ambiguous genitalia/malformations; Gonadal dysgenesis Intellectual disability CKD and/or proteinuria	45%–60% risk of developing Wilms tumor
WAGRO syndrome	Large deletion in chromosomal region extending beyond p13 to include deletion of <i>BDNF</i> gene on 11p14	Karyotype 46,XY or XX Features of WAGR syndrome along with childhood obesity and pancreatitis	45%–60% risk of developing Wilms tumor
Isolated nephrotic syndrome (excludes syndromic forms listed before)	Most common mutations are located at either exon 8 or 9. Many of the same mutations have been identified in patients with Denys-Drash	Karyotype 46,XY or XX Steroid-resistant nephrotic syndrome with diffuse mesangial sclerosis and/or FSGS <i>WT1</i> mutation identified in 2%–3% of all cases of isolated nephrotic syndrome not associated with developing Wilms tumor If accounting for all <i>WT1</i> mutations in steroid-resistant nephrotic syndrome then a mutation is identified 6%–8% of the time	N/A
Meacham syndrome	Mutations at either exon 8 or 9	Karyotype 46,XY: Undervirilization; abnormal internal female genitalia often double vagina Complex cyanotic heart lesions Hypoplastic left heart Hypoplastic lungs; diaphragmatic hernia/abnormalities	No reports of Wilms tumor, likely due to death in early infant/early childhood

Continued

TABLE. (Continued)

SYNDROME/DISEASE ASSOCIATED WITH <i>WT1</i> GENE MUTATION	SITE OF MUTATION IN THE <i>WT1</i> GENE ON CHROMOSOME 11P13	CLINICAL PHENOTYPE	TUMOR RISK
Wilms tumor	About 20% of patients with Wilms tumor have a <i>WT1</i> gene mutation	Karyotype 46,XY or XX Most common kidney cancer in the pediatric population Overall, 5th most common pediatric cancer 80% present with abdominal mass Overall, about 10% of Wilms tumor occurrences are associated with a syndrome (see above and below)	N/A
Syndrome/disease associated with increased risk of Wilms tumor, but not with <i>WT1</i> gene mutation	Site of mutation	Clinical phenotype	Tumor risk
Beckwith-Wiedemann syndrome	Mutation or epigenetic change at 11p15 region	Polyhydramnios Macroglossia Macrosomia Hemihyperplasia Omphalocele Anterior ear lobe crease Pits on the helix of the ear/linear ear fissures Neonatal hypoglycemia	20%–30% risk of developing Wilms tumor
Isolated hemi-hypertrophy syndrome	No causative mutation identified	1 side or 1 area of the body larger than the other	6% risk of developing Wilms tumor
Perlman syndrome	Mutation at 2q37 in <i>DIS3L2</i>	Macrosomia Deep-set eyes Kidney hamartomas	30% risk of developing Wilms tumor
Simpson-Golabi-Behmel syndrome	Mutation at Xq26 in <i>glypican-3</i>	Bulldoglike facies Polydactyly Heart disease	8% risk of developing Wilms tumor
Faconi anemia	Biallelic mutations at 13q12-13 in the <i>BRC42</i> gene	Microcephaly Short stature Hypoplastic/absent thumbs Café au lait lesions Hypogenitalia Cytopenia	20% risk of developing Wilms tumor
Sotos syndrome	Mutation at 5q35 in <i>NSD1</i> gene	Macrocephaly Macrosomia Large hands and feet Premature teeth eruption Poor coordination Variable intellectual ability	2%–3% risk of Wilms tumor

CKD=chronic kidney disease; ESKD=end-stage kidney disease; FSGS=focal segmental glomerulosclerosis; N/A=not applicable; WAGR=Wilms tumor, aniridia, genitourinary malformation, intellectual disability (formerly mental retardation); WAGRO=WAGR syndrome with childhood-onset obesity.

*XX karyotype has been reported, not generally associated with abnormal gonadal development, and therefore has a low risk for gonadoblastoma. However, the risk for Wilms tumor development is thought to remain high and on par with the XY karyotype.

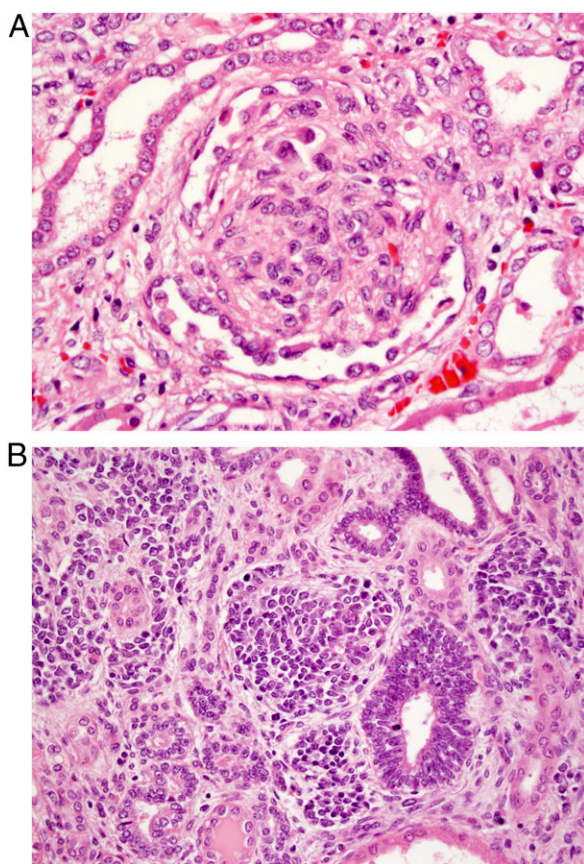


Figure. A. Representative glomerulus in a patient with a heterozygous missense variant, p.H445R in *WT1*, showing diffuse mesangial sclerosis (hematoxylin and eosin [H&E], $\times 600$). B. Representative interstitial region from the same patient with Denys-Drash syndrome demonstrating an intralobar nephrogenic rest, a precursor of Wilms tumor (H&E, $\times 400$).

- The same *WT1* mutation in one patient can present with a different phenotype or syndrome in another patient (Table).
- Genotypic females (XX) with mutations associated with DDS have a high risk of developing Wilms tumor, but are not thought to be at risk of developing gonadoblastoma.
- In DDS, prophylactic nephrectomy and gonadectomy should be performed to prevent the development of Wilms tumor or gonadoblastoma. The timing of the procedure remains controversial, but most would recommend performing before age 3 years.

- In differences of sex development, including ambiguous genitalia, the decision to raise the child as a boy or girl is best with family cooperation, a specialized multidisciplinary team, and ongoing psychological considerations.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the etiology of abnormal sexual differentiation.

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Case 3: Ambiguous Genitalia in a Newborn
Luke Viehl, Joseph P. Gaut, Raja Dandamudi and T. Keefe Davis
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Index of Suspicion in the Nursery

3 An Abnormal Nose Mass

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PRESENTATION

A term, small-for-gestational age (3rd percentile) Southeast Asian female infant is born at 39 1/7 weeks via uncomplicated, spontaneous vaginal delivery to a 36-year-old gravida 5, para 5 mother. The pregnancy is complicated by gestational hypothyroidism, which is treated with levothyroxine. Prenatal ultrasonography showed normal fetal anatomy at 20 weeks. At birth, her Apgar scores are 9 and 10 at 1 and 5 minutes, respectively. Examination reveals a healthy-appearing, small-for-gestational age female infant in no cardiopulmonary distress with the following facial deformities: 1) a 1-cm subcutaneous deep blue cystic soft tissue mass just medial to the medial canthus of the left eye; 2) soft tissue swelling of the nasal bridge; 3) mild right-sided deviation of the superior aspect of the nose with an anterior bony void between the nasal bone and nasal cartilage on palpation; and 4) bilateral upslanting palpebral fissures and hypertelorism (Fig 1). A well-lubricated 5-Fr feeding tube is easily passed through the left nare. The initial diagnosis is a large dacrocystocele with potential nasal bone fracture from birth trauma. No imaging is undertaken because the infant is in stable condition. She is discharged from the hospital with her mother on day 2 after birth.

Around 2 weeks of age, she is evaluated by an otolaryngologist for an enlarging of the mass. Magnetic resonance imaging identified a left-sided frontal periorbital meningoencephalocele with complex solid and cystic elements and compression of the medial left rectus muscle with lateral deviation of the left globe (Fig 2).

PROGRESSION

At 6 months of age, this infant underwent a single-staged surgical removal of the left-sided complex nasoethmoidal meningoencephalocele and facial reconstruction. She was followed by neurosurgery, craniofacial surgery, ophthalmology, and a complex care pediatrician alongside her primary pediatrician. Her surgical sites healed well. The pediatric ophthalmologist is closely following her for enophthalmos and suspected left-sided amblyopia secondary to the mass.

DISCUSSION

Frontoethmoidal encephaloceles are a rare form of encephaloceles, and have the highest incidence in the Southeast Asian population, as in this case, with a frequency as high as 1 in 5,000 according to some authors. (1) The etiopathogenesis is uncertain, with theories including toxin, pesticide, or mold exposure as potential causes. (2) Associations with parental age, birth order, religious affiliation, gestational diabetes, or maternal folic acid levels do not appear to be inciting factors during fetal development. (3)

AUTHOR DISCLOSURE Dr Van Heukelom has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Left-sided nasal mass at birth.

Embryologically, the ectoderm fails to separate from the neuroectoderm around the 4th week of gestation and an open neural tube defect develops with a persistent sub-arachnoid connection. (4) After partial neural tube closure, neural crest cells form and migrate anterolaterally around the developing orbital structure to complete the anterior

encephalocele by about the 8th week of gestation. (5) If the lesion involves only the meninges, then an encephalocele is formed, compared with a meningoencephalocele, which has concurrent brain matter, as seen in this case. (2) Any exposure to potential triggers must have occurred before this stage of embryogenesis.

Anatomically, frontoethmoidal encephaloceles herniate anteriorly through the cribriform plate at various locations. (6) They are divided into nasofrontal encephaloceles, which appear at the root of the nose above the level of the nasal bones; nasoethmoidal encephaloceles (most common), which are situated inferior to the nasal bones; and naso-orbital encephaloceles (least common), which are typically not visible but can cause upper airway obstruction. (1) In general, anterior (facial) encephaloceles encompass frontoethmoidal (sincipital) and basal encephaloceles, which herniate through the sphenoid sinus. (6) Anterior encephaloceles compose about 20% of all head encephaloceles compared with posterior (scalp) encephaloceles, which make up around 80%. (2)

CLINICAL FINDINGS

Most congenital frontoethmoidal encephaloceles are typically identified during routine prenatal ultrasonography or on initial newborn assessment. They typically 1) present with an internal midline cranial defect corresponding to the site of failed neural tube closure, 2) are covered with at least an epithelial layer, and 3) will present as a soft, palpable

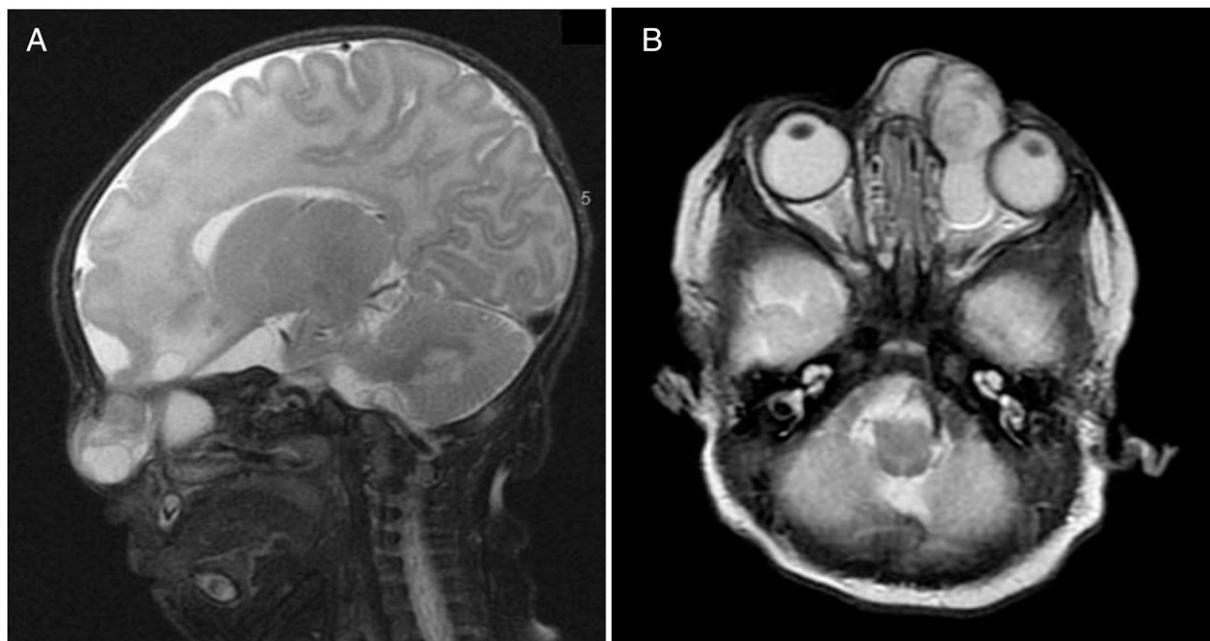


Figure 2. Magnetic resonance imaging scans. A. Sagittal view. B. Axial view.

mass. (1) They may transilluminate and can enlarge with an increase in cranial pressure such as crying or straining, or on application of the Valsalva maneuver. (2) The Furstenberg test, compression of the jugular veins, will also result in enlargement of the mass. (2) Ophthalmologic involvement includes hypertelorism, microphthalmia, strabismus, lacrimal duct obstruction, or decreased visual acuity. (7) Associated neural findings may include hydrocephalus (most common), microcephaly, anophthalmia, corpus callosum dysgenesis, or cortical atrophy. (4)

Maternal fetal α -fetoprotein levels are rarely elevated because of the presence of overlying epithelium. (8) Magnetic resonance imaging is the preferred mode of diagnosis because of its superior ability to evaluate the presence of intracranial involvement. (4) Adjunct facial computed tomography scans identify osseous involvement. (4)

DIFFERENTIAL DIAGNOSIS

Among nasal masses, encephaloceles are the most serious and need to be recognized early because of the potential risk for cerebrospinal fluid (CSF) leaks, meningitis, or intracranial abscess. (5) The differential diagnosis includes common nasal masses such as nasolacrimal duct mucoceles, hemangiomas, lipomas, pilomatricomas, and rarer masses such as dermoid/epidermoid cysts and nasal cerebral heteropias (formerly gliomas). (4)

TREATMENT

A single-staged combined craniofacial approach is the surgery of choice. (7) Meticulous planning with a multidisciplinary team is crucial. (6) Delayed surgical intervention until at least 6 months of age in stable children allows for growth of the facial structures and fewer anesthesia complications. (7)

Surgical goals are to provide a watertight closure of the dural defect at the skull along with craniofacial reconstruction and closure of any bony defects. (1) Untreated hydrocephalus may result in postoperative CSF leaks and must be corrected with a ventriculoperitoneal shunt before definitive surgery. (9) Intraoperative complications include blood loss, hypothermia, and electrolyte disturbances. (7)

OUTCOMES

Outcomes are quite favorable for children with frontoethmoidal encephaloceles. With the absence of brain damage or herniation, normal intelligence and motor development can be achieved in most patients. (9) The poorest prognosis

involves patients with associated hydrocephalus or congenital brain anomalies such as microcephaly. (1) Nasal encephaloceles carry a low mortality, whereas surgery-related mortality is about 3%. (2) Deaths are typically secondary to postoperative complications such as meningitis or aspiration pneumonias. (2)

Lessons for the Clinician

- Although rare, nasal encephaloceles need to be recognized early with appropriate evaluation and referral.
- There is a definite regional/ethnic predilection for those of Southeast Asian descent with uncertain etiopathogenesis.
- With isolated nasal encephaloceles and an appropriate multidisciplinary surgical team approach, outcomes are quite favorable.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the embryology, prevention, incidence, and differential diagnosis of myelomeningocele and encephalocele.
- Know the clinical and imaging findings, treatment, and outcome of myelomeningocele and encephalocele.

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Case 3: An Abnormal Nose Mass

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Case 3: An Abnormal Nose Mass

Jesse G. Van Heukelom

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Index of Suspicion in the Nursery

1 An Enigma of Recurrent Extubation Failure in a Neonate

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PRESENTATION

A 10-day-old male neonate is referred in view of inability to wean off respiratory support. The infant is born through assisted breech delivery with a birthweight of 2.75 kg to a gravida 2 woman. Antenatal history is not significant. However, there is meconium staining of the amniotic fluid. The infant did not cry after birth and his Apgar scores are 3 and 6 at 1 minute and 5 minutes, respectively. He has cyanosis and tachypnea soon after birth requiring intubation. Vital signs at admission include a temperature of 97.7°F (36.5°C), heart rate of 155 beats/min, capillary refill time of 2 seconds, and saturation of 94% on ventilator. The infant's activity is diminished, with poor tone in all 4 limbs.

The possibilities considered at this stage are perinatal asphyxia, meconium aspiration syndrome, congenital pneumonia, congenital heart disease, sepsis, and persistent pulmonary hypertension of the newborn.

Initial investigations indicate negative sepsis screen (total white blood cell count 20,000/ μ L [20×10^9 /L], C-reactive protein <6 mg/L [57.1 nmol/L], absolute neutrophil count 15,800/ μ L [15.8×10^9 /L]); normal blood glucose (98 mg/dL [5.4 mmol/L]); hemoglobin 10.7 g/dL (107 g/L); ionized calcium 4.8 mg/dL [1.2 mmol/L]; and normal blood gas analysis (pH 7.37, P_{CO_2} 39 mm Hg [5.2 kPa], P_{O_2} 73 mm Hg [9.7 kPa], bicarbonate 22 mEq/L [22 mmol/L]). Chest radiography shows normal lung fields bilaterally with fracture of right clavicle (Fig 1).

NOTE The editors and staff of NeoReviews find themselves in the fortunate position of having too many submissions for the Index of Suspicion in the Nursery column. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will make an announcement in NeoReviews when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

AUTHOR DISCLOSURE Drs Romana, Rajarathinam, Bandiya, Shinde, Shivanna, and Benakappa have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Radiograph showing normal position of diaphragm (on ventilator).

CASE PROGRESSION

The infant is maintaining saturation with minimal pressures on synchronized intermittent positive pressure ventilation, and hence extubation is planned. He has minimal spontaneous respiratory efforts (respiratory rate 20 breaths/min) and develops cyanosis and bradycardia within minutes of extubation, leading to reintubation. However, there is no increase in pressure and oxygen requirement. Bronchoscopy performed to rule out congenital malformations of the airway and lung has a normal result. A trial of extubation is considered, which failed twice in an interval of 48 hours.

At this stage, it is decided to again review the history and clinical examination findings to ascertain the cause for recurrent extubation failure. Characteristic posture noted in the upper limbs was adduction, internal rotation of arm with pronation, and extension at elbow joint. This was suggestive of Erb palsy. There is no movement of the upper limbs with hypotonia, power of 1/5 (grading on the Medical Research Council Scale for Muscle Strength), and absent biceps and triceps jerk. On the contrary, posture, tone, power, and reflexes are normal in the lower limbs. Also, the infant has normal sensorium. Repeat chest radiography at this stage reveals elevated bilateral diaphragms, more on the right side. In the background of difficult delivery, this correlates with birth injury, leading to phrenic nerve injury and bilateral diaphragmatic palsy. (Fig 2) Magnetic resonance imaging and



Figure 2. Radiograph showing elevated right hemidiaphragm (after tracheostomy).



Figure 3. Magnetic resonance imaging scan showing injury to spinal cord.

computed tomography of the spine reveal C3-C5 root avulsion injury leading to pseudomeningocele (Figs 3–5). In view of prolonged respiratory support, tracheostomy is planned.



Figure 4. Magnetic resonance imaging scan showing injury to spinal cord.

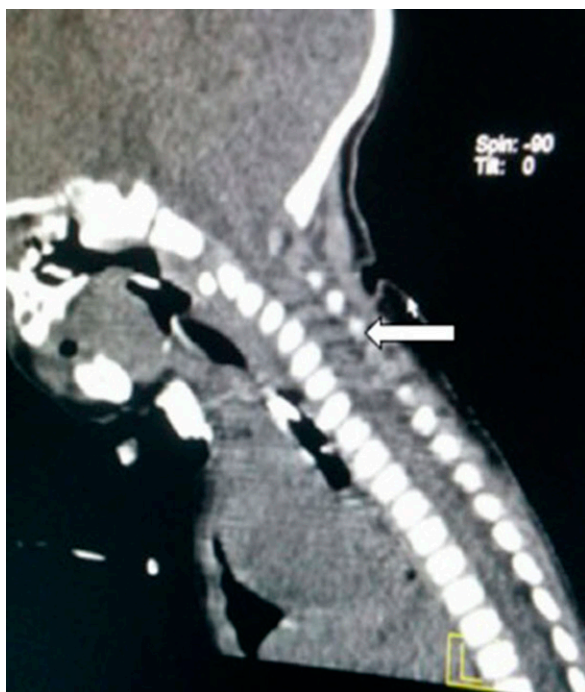


Figure 5. Computed tomography scan showing cervical injury.

Diaphragmatic plication is done on the right side. He undergoes ventilation for a period of approximately 45 days. During this course, he develops spontaneous movements of the left upper limb, with the power increased to 3/5, with no improvement on the right side. The infant is weaned to continuous positive airway pressure (CPAP) 5 days after surgery and then to room air. He is discharged at 3 1/2 months of age. At the time of discharge, he is active, alert, accepting feeds well, and gaining weight with minimal distress.

DISCUSSION

Birth injuries are a diverse set of conditions occurring in a neonate because of a traumatic event during the process of delivery. (1) Diaphragmatic palsy resulting from phrenic nerve injury is a relatively uncommon form of birth injury, but nearly 80% to 90% of cases have associated brachial plexus injury. (2) Isolated diaphragmatic palsy is uncommon, with a prevalence of about 0.14 per 1,000 live births. (3)

Apart from birth injury, other common etiologies include iatrogenic (cardiothoracic surgery, invasive cannulation) and neuromuscular disorders. Injury to the phrenic nerve during cardiovascular surgery is the most common cause followed by birth injury. (4)

Injury to the phrenic nerve and spinal cord occurs because of excessive traction placed on the spine during delivery of the shoulder in a cephalic presentation and delivery of the head in a breech presentation. (2) The risk of injury is higher during the neonatal period because of ligament laxity, weak musculature, and incomplete mineralization of the vertebrae. (3)

Diaphragmatic palsy following birth injury is most commonly unilateral (right>left). Bilateral involvement, which occurs in less than 10% of cases, is seen in neonates with severe birth injury. (5)(6) In the current case, the birth injury was severe enough to cause bilateral diaphragmatic palsy.

Diaphragmatic palsy should be suspected when there are recurrent failed extubation attempts in the background of a traumatic delivery, especially with breech presentation. Affected neonates can have decreased chest movement on the affected side, with corresponding increased movement on the unaffected side and paradoxical chest movement. (7)

Because most of these neonates receive positive pressure ventilation, clinical and radiologic findings can be easily obscured, as in our case. Elevated hemidiaphragm, which is usually seen in these cases, may not be present if the neonate is receiving positive pressure ventilation. (2) Ultrasonography is the preferred method because it is safe, does not carry any risk of radiation exposure, and can be done serially to assess the diaphragmatic function. (8)

Management includes supportive care in the form of supplemental oxygen, nasal CPAP, and mechanical ventilation depending on the severity. CPAP has been shown to be beneficial in some patients and a trial should be given in every neonate because it avoids intubation. (2)

Surgical intervention should be considered usually after 1 to 2 months of positive pressure ventilation when there is no recovery. (2) Surgical plication of the affected diaphragm is the commonly performed procedure and a satisfactory response is seen in most cases. (9)

Phrenic nerve stimulation may help in making a decision regarding surgery, with prolonged conduction latencies or reduction in amplitude or absence of diaphragmatic action potentials indicating poor chances of spontaneous recovery. (10)

In the current case, the main presentation was recurrent extubation failures with minimal ventilator settings and normal sensorium. This infant also had bilateral Erb palsy, which led us to evaluate for associated phrenic nerve injury because of the spinal cord trauma leading to diaphragmatic palsy.

Lessons for the Clinician

- Diaphragmatic palsy should be considered in neonates in cases of recurrent extubation failures, especially if it is associated with a history of abnormal presentation or traumatic delivery.
- All cases of Erb palsy with respiratory distress or extubation failures should be evaluated for associated phrenic nerve injury.
- Clinical and radiologic signs of diaphragmatic palsy can be missed in a neonate receiving positive pressure ventilation.
- Imaging of the spine is recommended to rule out other associated injuries.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical features and prognosis of birth injuries, such as fractures, lacerations, and facial palsies.

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Case 1: An Enigma of Recurrent Extubation Failure in a Neonate
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Index of Suspicion in the Nursery

1 An Infant with Arm Swelling and Nodules

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PRESENTATION

A male neonate is born via spontaneous vaginal delivery to a 28-year-old primiparous woman at 39 2/7 weeks of gestation after an uncomplicated pregnancy. Labor is complicated by prolonged fetal heart rate decelerations, but the mother declines a cesarean section and vacuum extraction is initially unsuccessful. At birth the neonate is apneic but maintains a heart rate greater than 100 beats/min throughout the resuscitation. He requires intubation for persistent apnea 4 minutes after birth. His Apgar scores are 2, 3, 5, and 5 at 1, 5, 10, and 20 minutes, respectively. His physical examination on admission to the NICU is significant for diffuse hypotonia, lethargy, and absence of primitive reflexes. His arterial blood gas measurement 1.5 hours after birth shows a pH of 7.32, P_{CO_2} of 32 mm Hg, and base deficit of 9. A blood culture specimen is collected and he starts empiric treatment with ampicillin and gentamicin.

The infant is transferred to a tertiary care NICU for therapeutic hypothermia and has moderate encephalopathy on admission. He has a fluctuant, boggy mass over his occipital skull and undergoes noncontrast head computed tomography, which shows a large subgaleal hemorrhage, skull fracture, and small ventricles concerning for cerebral edema. A significant drop in his hematocrit is noted, and he receives transfusions of packed red blood cells and fresh frozen plasma. He requires a dopamine infusion and stress-dose hydrocortisone to maintain age-appropriate blood pressures.

Electroencephalography (EEG) shows electrographic and clinical seizure activity, which is treated with phenobarbital and levetiracetam. He also receives a midazolam infusion for agitation while cooling.

He undergoes rewarming after 72 hours of therapeutic hypothermia. He is gradually weaned to room air and has no further seizures. He remains in the NICU while working on oral feeding skills. One month after admission, he is noted to have swelling of his left hand and forearm. Physical examination shows a scab on the back of the left hand, soft tissue swelling of the forearm, and palpable nodules along the metacarpals, wrist, and ulnar side of the forearm. Radiography shows extensive vascular calcifications and faint nodular calcifications of the dorsum of the wrist and hand (Fig 1). Magnetic resonance imaging demonstrates wall thickening and surrounding enhancement of the cutaneous venous structures. This shows enhancement of the subcutaneous soft tissues, myositis, and solid nodules with inflammatory changes over the dorsal hand and wrist (Fig 2).

DISCUSSION

Diagnosis

Based on the imaging findings, the differential diagnosis includes skin and vascular calcification due to calcium gluconate infusion, subcutaneous fat

AUTHOR DISCLOSURE Drs Pavlek and Braswell have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. A left arm radiograph demonstrates extensive vascular calcifications and nodular calcifications over the wrist and hand.

necrosis, or hypercalcemia. This presentation is consistent with calcinosis cutis, which is a condition in which insoluble calcium phosphate salts are deposited in the skin and subcutaneous soft tissue. (1) To evaluate for further vascular involvement, radiographs of the chest, abdomen, and right upper extremity are obtained and are normal. The serum calcium concentration on the day of the imaging is only mildly elevated at 10.7 mg/dL (2.7 mmol/L). Review of the medical record reveals that the infant received a dose of calcium gluconate via peripheral intravenous administration in the left hand during therapeutic hypothermia. Other medications



Figure 2. Magnetic resonance imaging scan of the left arm shows phlebitis, myositis, enhancement of the subcutaneous soft tissues, and solid nodules with inflammatory changes over the wrist and hand.

administered intravenously via the left hand included 10% dextrose in water, 0.9% sodium chloride, dopamine, gentamicin, ampicillin, phenobarbital, midazolam, and levetiracetam.

The Condition

Several mechanisms for the development of calcinosis cutis have been suggested, including:

- An increase in cell membrane permeability resulting from local tissue injury, allowing an influx of calcium into the cytosol. The capacity for mitochondria to sequester calcium and phosphorus is exceeded, causing precipitation of calcium phosphate in the cytosol.
- Local tissue damage causing release of alkaline phosphatase, which increases the tissue pH and facilitates calcium phosphate salt precipitation.

- Fat cell necrosis because of local tissue damage leading to release of free fatty acids, which bind with calcium ions and form calcium soaps.

Local tissue injury often results from extravasation of intravenous medications, phlebitis, and repeated attempts to insert an intravenous line. (2)

This condition is divided into 5 subtypes, based on the underlying etiology:

- Dystrophic: Due to local tissue damage, with normal serum calcium and phosphorus levels.
- Metastatic: Due to abnormal calcium or phosphate metabolism, which causes calcium salts to precipitate in otherwise normal soft tissues.
- Iatrogenic: Calcium deposition into the skin as an adverse effect of medical therapy.
- Calciphylaxis: Calcification of small and medium arteries in the dermis and subcutaneous tissues, often in the setting of end-stage renal disease or malignancy.
- Idiopathic: Calcium deposition without any underlying metabolic abnormalities or tissue damage. (3)

Previous case studies have described calcification of the hepatic vein in the setting of calcium gluconate administration via umbilical vein catheter (UVC), improper positioning of the UVC, and use for more than 7 days. (4) Many case reports include patients with iatrogenic calcinosis cutis after extravasation of a calcium gluconate or calcium chloride infusion. (5) Iatrogenic calcinosis cutis has also been reported on the heels of infants who had multiple heel sticks for laboratory collection and at the sites of EEG lead placement. (1)(6)

Dystrophic calcinosis cutis can rarely be seen in the NICU at the sites of subcutaneous fat necrosis after therapeutic hypothermia or in the setting of an intrauterine herpes simplex virus infection. (7) Metabolic calcinosis cutis can be seen in neonates with rhabdomyolysis, renal failure, and pseudohypoparathyroidism. (2) No other cases of peripheral vein calcification in the setting of calcium gluconate administration are reported in the literature.

Treatment

Most cases of calcinosis cutis are expected to resolve within 8 weeks. (3) Heel stick calcinosis cutis has been reported to self-resolve in 18 to 30 months, though persistent, painful, or ulcerating lesions can be surgically excised. (6) In complicated cases of calcium extravasation involving a large area, skin grafting may be required. One case report even described compartment syndrome requiring fasciotomy as a complication of a calcium gluconate extravasation. (5) Management of the



Figure 3. A follow-up left arm radiograph 6 weeks after diagnosis shows complete resolution of the vascular calcifications.

underlying disease is needed for patients with metabolic calcinosis cutis in the setting of hypercalcemia or hyperphosphatemia. (8)

The current patient did not receive any treatment for his calcinosis cutis. Follow-up radiography performed 6 weeks after the initial diagnosis demonstrated complete resolution of the calcifications (Fig 3).

Lessons for the Clinician

- Peripheral administration of calcium-containing fluids has the risk of extravasation and tissue injury, leading to calcinosis cutis.
- Hepatic and portal vein calcification can be seen in patients receiving calcium-containing fluids via the umbilical vein catheter.

- Calcinosis cutis can be a complication of multiple heel sticks or intravenous catheter placement attempts in the NICU.
- Calcinosis cutis is typically a self-limited condition in neonates and rarely requires treatment in neonates.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the causes and clinical manifestations of catheter complications of parenteral nutrition.
- Recognize the causes and clinical manifestations of metabolic complications of parenteral nutrition.
- Recognize the potential toxicities associated with the use of parenteral nutrition.
- Know the etiology and clinical manifestations of neonatal hypercalcemia.

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Case 1: An Infant with Arm Swelling and Nodules

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Index of Suspicion in the Nursery

2 An Infant with Poor Weight Gain and Persistent Tachycardia

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AUTHOR DISCLOSURE Drs Krasaelap and Kannikeswaran have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

CASE PRESENTATION

An 8-week-old-term female infant presents with a 2-day history of nasal congestion, cough, and difficulty breathing. The mother denies fever and any change in feeding or wet diapers. Initial vital signs show a rectal temperature of 99.8°F (37.7°C), heart rate of 190 to 210 beats/min, respiratory rate of 70 to 80 breaths/min, oxygen saturation of 95% in room air, and blood pressure of 128/78 mm Hg. The patient is noted to be small for age (3,650 g, 7th percentile) with normal height and head circumference. She is in moderate respiratory distress with intercostal retractions but clear lungs. She is tachycardic, with good pulses and perfusion. No murmurs, gallop, or organomegaly were noted. She is administered aerosolized albuterol/ipratropium, high-flow oxygen through nasal cannula, and 20 mL/kg of normal saline bolus, with minimal improvement in cardiorespiratory status. Results of chest radiography and capillary blood gas measurement are normal. The nasal swab is positive for respiratory syncytial virus. The patient is transferred to the pediatric intensive care unit for respiratory syncytial virus bronchiolitis.

Patient was born at 38 weeks to a 27-year-old gravida 3, para 3-0-0-3 mother, who reported regular prenatal care without any medical problems. The infant's birthweight was appropriate for gestational age (3,430 g). However, after discharge, her weight gain was poor (<2 g/day) despite absence of feeding difficulty and change to a concentrated formula (25 calorie/ounce).

During her admission to the intensive care unit, respiratory distress and tachycardia persist despite the administration of 3 additional 20-mL/kg fluid boluses. Serial capillary blood gases are unremarkable. Electrocardiography shows sinus tachycardia without pre-excitation pathway. Blood culture is negative. Echocardiography and abdominal ultrasonography are also unremarkable.

The infant's respiratory status normalizes on hospital day 3, but she remains tachycardic, with a heart rate of up to 180 beats/min. She tolerates high-calorie formula well but no significant weight gain is observed (6 g/day). Results of thyroid function tests (TFTs) are consistent with hyperthyroidism (thyrotropin [TSH] <0.008 μ IU/mL, free thyroxine [fT_4] 5.2 ng/dL [66.9 pmol/L]).

Review of maternal records revealed that the mother was diagnosed with Graves' disease (GD) at 8 weeks of pregnancy. Maternal TFTs at 18 weeks showed an elevated fT_4 (8.1 ng/dL [104 pmol/L]) with an undetectable TSH level. Thyroid-stimulating immunoglobulin (TSI) was significantly elevated (>500%). Though asymptomatic, she was started on treatment with methimazole. Serial fetal ultrasonography showed normal growth and anatomy. Serial nonstress test showed normal baseline fetal heart rate of 110 to 160 beats/min, with normal

variability and accelerations. Last maternal TFTs 1 month before delivery showed normalized fT_4 with a suppressed TSH level.

Given the history of maternal GD, the patient's poor weight gain, and laboratory results consistent with hyperthyroidism, a diagnosis of neonatal hyperthyroidism is made.

CASE PROGRESSION

The patient started treatment with methimazole 0.5 mg/kg per day and propranolol 0.5 to 1 mg/kg per day as recommended by the endocrinologist. Two days after therapy, her heart rate normalized to 120 to 140 beats/min and weight gain improved to 60 g/day.

At the 2-week follow-up, the patient continued to demonstrate excellent weight gain (35 g/day). Resting heart rate was 130 beats/min. Repeat TFTs showed normalized fT_4 and TSH levels with elevated TSI (216%), consistent with neonatal hyperthyroidism.

DISCUSSION

The prevalence of GD in pregnancy is 0.2%. Neonatal hyperthyroidism occurs in 1% to 12.5% of these pregnancies, whereas 3% of pregnancies result in asymptomatic hyperthyroidism, (1) resulting in a prevalence of neonatal hyperthyroidism between 1 in 4,000 and 1 in 50,000 pregnancies. (1)

Neonatal hyperthyroidism is usually secondary to transplacental passage of TSI, a type of thyroid receptor antibody, from a mother with an autoimmune thyroid disorder. This causes transient hyperthyroidism secondary to limited clearance of maternal TSIs from the infant's circulation until 8 to 20 weeks. (1) Thyroid hormone levels usually normalize by 48 weeks after birth. (2) Less common forms causing persistent neonatal hyperthyroidism are secondary to

dominantly inherited TSH receptor mutations (3) and mutations of the stimulating G protein in McCune-Albright syndrome. (4) Risk factors for developing neonatal hyperthyroidism are summarized in Table 1. (1)

Signs and symptoms of fetal and neonatal hyperthyroidism (Table 2) are nonspecific and can be confused with sepsis or heart disease. Symptoms usually manifest by 10 days after birth, (5) but can be apparent after birth or delayed up to 45 days. (6) Mortality rates can be as high as 12% to 20% in undiagnosed hyperthyroidism due to heart failure,

TABLE 2. Signs and Symptoms of Fetal and Neonatal Hyperthyroidism

Fetal
Intrauterine growth restriction
• Prematurity
• Fetal tachycardia (heart rate >160 beats/min)
• Fetal goiter
• Nonimmune hydrops from cardiac failure
• Intrauterine death
Neonatal
• Persistent acrocyanosis
• Goiter, tracheal obstruction
• Periorbital edema, lid retraction, and exophthalmos
• Tachycardia, arrhythmia, congestive heart failure, systemic/pulmonary hypertension
• Microcephaly, craniosynostosis, frontal bossing, triangular-shaped face
• Advanced bone age
• Irritability, jitteriness, and restlessness
• Diaphoresis, flushing
• Excessive appetite
• Frequent vomiting and diarrhea
• Hypoglycemia
• Poor weight gain
• Hyperbilirubinemia, hepatic cholestasis
• Hepatosplenomegaly (with or without congestive heart failure)
• Hyperviscosity syndrome
• Thrombocytopenia, petechiae
• Lymphadenopathy
• Infections
• Death

TABLE 1. Neonates at High Risk for Neonatal Hyperthyroidism

Mothers with clinical thyrotoxicosis or those receiving thionamide therapy during third trimester
Elevated maternal thyroid-stimulating immunoglobulins (>2-3 times normal) between 20 and 24 weeks of pregnancy
Mothers with a previous infant with neonatal hyperthyroidism
Family history of thyrotropin receptor mutation
Evidence of fetal thyrotoxicosis

and less commonly due to tracheal compression, infections, and thrombocytopenia. (1) Long-term effects of undiagnosed hyperthyroidism include craniosynostosis, intellectual impairment, and growth restriction.

Newborn screening is not a reliable measure to detect infants with hyperthyroidism because it is designed to detect elevated TSH levels seen in primary hypothyroidism. Testing for neonatal hyperthyroidism in infants of mothers with GD depends on the maternal TSI levels. No testing is recommended for those infants whose maternal TSIs are negative. If maternal TSIs are positive or unavailable, cord blood should be tested. Low- or high-risk infants with normal cord blood TSI can be discharged and no specific follow-up is needed. (7) If cord blood TSI is abnormal, TFTs should be measured at 3 to 5 days after birth unless clinical signs warrant earlier testing. If initial TFTs are normal, it is repeated between days 10 and 14, and at 4 weeks and 2 to 3 months to identify infants with delayed-onset hyperthyroidism. (7)

Treatment of asymptomatic infants with hyperthyroidism remains controversial. (7) Symptomatic infants should be treated, given the long-term effects of hyperthyroidism and low risk of medication-induced hypothyroidism. (1)(7) The mainstay of treatment is methimazole with an initial dose of 0.625 mg twice daily (0.4 mg/kg per day) for a term newborn. (7) Methimazole is preferred over propylthiouracil because of the latter's association with liver failure. Methimazole acts by blocking thyroid hormone synthesis and hence clinical effects might be delayed until thyroid hormone storage is depleted. A strong iodine solution (Lugol solution 1 drop every 8 hours or potassium iodide 1 drop daily) can be added to block the immediate release of hormone in severe cases. Prednisolone, 2 mg/kg per day, can be added to suppress the deiodination process and replenish glucocorticoids during the hypermetabolism period. In patients with severe sympathetic overstimulation, propranolol 2 mg/kg per day in 2 divided doses for 1 to 2 weeks can be added. (7)

Infants receiving treatment need weekly follow-up until symptoms and TFTs stabilize, and every 2 weeks thereafter. (7) Most infants require medical treatment for 4 to 8 weeks, while those with persistent neonatal

hyperthyroidism secondary to TSH mutations may require ablative treatment.

Lesson for the Clinician

- Neonatal hyperthyroidism is a rare condition but can result in serious morbidity or even death in infants if undiagnosed. This diagnosis should be considered, particularly in infants born to mothers with autoimmune hyperthyroidism with elevated thyroid-stimulating immunoglobulin.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the relationship between fetal and maternal thyroid physiology.
- Identify the etiology, clinical manifestations, laboratory features, and management of neonatal thyrotoxicosis.

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Case 2: An Infant with Poor Weight Gain and Persistent Tachycardia

Amornluck Krasaelap and Nirupama Kannikeswaran

NeoReviews 2017;18:e389

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Index of Suspicion in the Nursery

3 An Infant with Severe Dehydration, Weight Loss, and Abnormal Newborn Screening Test Results

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AUTHOR DISCLOSURE Drs Was, Lee, Nally, and Arain have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is born at 37 weeks' gestation via vaginal delivery to a gravida 4, para 3 woman. The woman's pregnancy and delivery are uncomplicated. The infant's birthweight is 2,680 g. She is discharged from the hospital in good condition; at home, she breastfeeds well and gains weight appropriately; on day 10, her weight is 2,778 g (4% above birthweight).

On day 12, the mother notes that the infant has begun to breastfeed poorly. On day 14, formula feeding is attempted, but her intake remains poor, with an associated decrease in urine output. On day 16, she presents to an outpatient clinic, where she appears cachectic and severely dehydrated but responsive. Her weight is 1,760 g, a decrease of more than 1 kg (37%) from 6 days ago. She is transferred to the NICU for further evaluation and treatment.

The infant's newborn screening results from day 1 are normal; however, repeat newborn screening performed on day 10 shows an abnormality in the fatty acid oxidation profile, with malonyl carnitine levels of 0.68 $\mu\text{mol/L}$ (normal $\leq 0.5 \mu\text{mol/L}$). The patient's initial laboratory tests were notable for the following results: sodium, 174 mEq/L (174 mmol/L); potassium, 7.2 mEq/L (7.2 mmol/L); chloride, 141 mEq/L (141 mmol/L); bicarbonate, 7 mEq/L (7 mmol/L); blood urea nitrogen, 273 mg/dL (97 mmol/L); creatinine, 5.61 mg/dL (428 $\mu\text{mol/L}$); glucose, 1,266 mg/dL (70.2 mmol/L); anion gap, 31 mEq/L (31 mmol/L); lactate, 40.5 mg/dL (4.5 mmol/L); ammonia, 83 $\mu\text{g/dL}$ (59 $\mu\text{mol/L}$); β -hydroxybutyrate, 3.1 mmol/L (reference range 0.2–2.8 mmol/L); serum osmolality, 433 mOsm/kg (433 mmol/L); white blood cells, 9,500/ μL ($9.5 \times 10^9/\text{L}$); hemoglobin, 19.7 g/dL (197 g/L); platelets, $33 \times 10^3/\mu\text{L}$. C-peptide level was 1.1 ng/mL (0.36 nmol/L; reference range 0.8–4 ng/mL [0.26–1.32 nmol/L]) when blood glucose was 477 mg/dL (26.4 mmol/L) while receiving an intravenous insulin infusion. Subsequent therapeutic intervention confirmed the diagnosis.

DISCUSSION

Diagnosis

The patient required an intravenous insulin infusion of up to 0.04 U/kg per hour (~ 1 U/kg per day) for treatment of severe hyperglycemia. She received fluid resuscitation for dehydration and correction of hypernatremia. The hypernatremia was attributed to severe dehydration from osmotic diuresis due to glycosuria. Over the course of several days, with insulin infusion and fluid restoration, her electrolytes and glucose levels stabilized (Figure).

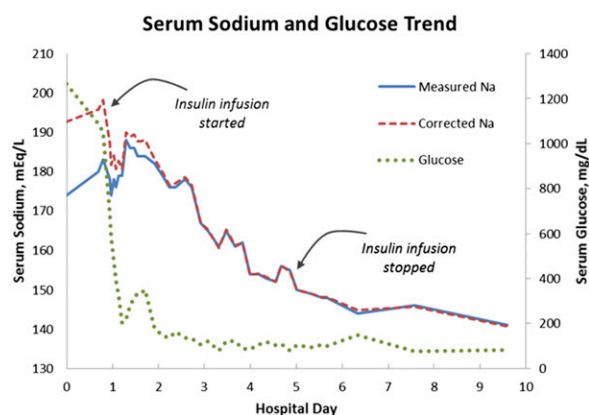


Figure. Serum sodium (Na) and glucose trend.

The infant received platelet and blood transfusions for thrombocytopenia and anemia. She developed rhythmic movements concerning for seizures and received lorazepam for treatment, but subsequent analysis with electroencephalography did not reveal seizure activity. The patient had no recurrence of symptoms. She was able to breastfeed and maintain normal glucose levels without administration of exogenous insulin, and was discharged in stable condition. Result of genetic testing for neonatal diabetes mellitus (DM) was negative. Diabetes autoantibodies in the infant and mother were negative.

The Condition

Neonatal DM is a rare metabolic disorder that usually presents in the first 6 months after birth; it is defined as persistent hyperglycemia in the first months after birth, which lasts at least 2 weeks and requires management with insulin. (1) The incidence of neonatal DM is approximately 1 in 300,000 to 400,000 newborns. Most cases of neonatal DM are monogenic in nature and result in poor insulin production. Clinically, patients are placed into 2 categories: transient and permanent. In transient neonatal DM, symptoms resolve during infancy, though there is a 50% chance for recurrence later in life. (2) In permanent neonatal DM, symptoms persist, and management depends on exogenous insulin. (3) The clinical presentation of hyperglycemia and low insulin may be accompanied by findings such as failure to thrive, dehydration, and/or ketoacidosis, as was seen in this patient. (4)

The case represents a nonclassic presentation of diabetes in early infancy with a negative genetic evaluation. The time frame of her hyperglycemia is unclear based on clinical history; however, the duration likely was longer than the 4 days during which she required insulin. Endogenous insulin production was present based on the detectable C-peptide level, though it was insufficient to overcome hyperglycemia. The C-peptide level confirmed that the infant

was able to produce a very small amount of insulin, and that she did not have complete insulin deficiency. The patient's clinical course and history of low birthweight at term supports the diagnosis of transient neonatal DM; however, genetic evaluation for the most common causes of this condition was unrevealing. Unusual aspects of her presentation included the severity of hyperglycemia, with glucose levels up to 1,200 mg/dL (67 mmol/L), which was likely related to dehydration and poor renal perfusion. The serum osmolality was significantly elevated, suggesting a presentation of hyperosmolar hyperglycemia. The clinical picture of hypernatremia, hyperosmolality, hyperglycemia, and severe dehydration raises the possibility of Wolfram syndrome as a diagnosis, which involves DM, diabetes insipidus, anemia, and thrombocytopenia. (5) This particular case lacked the characteristics of hearing loss and optic atrophy, which could develop later in life.

Insulin administration and high caloric intake are crucial to ensure adequate growth in such patients. Total body water deficit should be slowly corrected to euvolemia, to prevent rapid fluid and electrolyte shifts. Because glucose predominantly exists in extracellular fluid, hyperglycemia results in extracellular hyperosmolality, which requires osmotic equilibration achieved by water abstraction. Hyperglycemia, therefore, is known to depress serum sodium concentration. To accurately assess and manage sodium abnormalities, serum sodium levels should be corrected by using the Katz formula (6):

$$\text{Corrected Sodium (in mEq/L)} = \text{Measured Sodium (in mEq/L)} + 0.016 \times (\text{Glucose [in mg/dL]}) - 100$$

Hyperglycemia should be corrected slowly to avoid rapid changes in osmolality. Similarly, serum sodium should be corrected at a rate of 0.5 mEq/L per hour, because of the risks of cerebral edema and seizures associated with rapid correction of hypernatremia. (7) Serum electrolytes and pH should be measured regularly during treatment of neonatal DM and ketoacidosis, to monitor for concurrent alterations of serum potassium, magnesium, calcium, bicarbonate, or phosphorus. (8)

Lessons for the Clinician

- Abnormal newborn screening test results should be interpreted with caution and relative to the clinical context. Alternative metabolic disease processes can cause false-positive results.
- Neonatal diabetes mellitus may present with severe dehydration, acidosis, and electrolyte abnormalities, which should be corrected slowly because of the danger of significant and rapid changes.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the impact on water requirements of renal and metabolic fluid disorders associated with endocrine dysfunction in infants.
- Know how to manage electrolyte abnormalities in the neonate.
- Know the causes, including genetic and autogenic disorders, of neonatal hyperglycemia, including transient diabetes mellitus.
- Know the clinical and laboratory features and approach to therapy of neonatal hyperglycemia, including transient diabetes mellitus.

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Parent Resources from the AAP at HealthyChildren.org

- **Newborn Screening Tests:** <https://www.healthychildren.org/English/ages-stages/baby/Pages/Newborn-Screening-Tests.aspx>
- For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

Case 3: An Infant with Severe Dehydration, Weight Loss, and Abnormal Newborn Screening Test Results

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Index of Suspicion in the Nursery

1

An Infant with Skeletal Abnormalities and Facial Dysmorphisms

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PRESENTATION

AUTHOR DISCLOSURE Drs Kwak, Grady, and Derrick have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A male infant is born at 29 5/7 weeks' gestation via vaginal delivery to a 35-year-old gravida 2 para 1 mother with limited prenatal care. His mother initially presents at a referring hospital in preterm labor, where she is given a dose of betamethasone and then transferred. On admission, prenatal laboratory tests are performed. Labor is augmented due to a 7-cm dilation. The infant's birth measurements are as follows: weight, 1,530 g (68th percentile); length, 35 cm (3rd percentile); and head circumference, 27.5 cm (45th percentile). His Apgar scores are 8 at 1 minute and 9 at 5 minutes. His physical examination findings are notable for musculoskeletal abnormalities, including limited extension at the elbows bilaterally and an internally rotated left shoulder. He is also noted to have slightly anteverted nares and a depressed nasal bridge. On abdominal examination, he has slight distention but no hepatosplenomegaly. No skin rashes are noted. After delivery, he has intermittent respiratory distress that improves with stimulation. Due to his low oxygen saturation values and increased work of breathing, he is first started on continuous positive airway pressure and then undergoes intubation to improve saturations. Laboratory evaluation consists of a complete blood cell (CBC) count and liver function tests, which show the following: white blood cell (WBC) count, $30.9/\mu\text{L}$ ($0.03 \times 10^9/\text{L}$); hemoglobin, 11.4 g/dL (114 g/L); hematocrit, 35% (0.35); platelets, $106 \times 10^3/\mu\text{L}$ ($106 \times 10^9/\text{L}$); alkaline phosphatase, 301 U/L ($5.03 \mu\text{kat/L}$); alanine aminotransferase, 15 U/L ($0.25 \mu\text{kat/L}$); aspartate aminotransferase, 65 U/L ($1.09 \mu\text{kat/L}$); and direct bilirubin, 1.4 mg/dL ($24 \mu\text{mol/L}$). A lumbar puncture is performed, with cerebrospinal fluid (CSF) results showing a glucose concentration of 53 mg/dL (3 mmol/L), protein of 116 mg/dL, red blood cell count of $10.8 \times 10^6/\mu\text{L}$ ($10.8 \times 10^{12}/\text{L}$), and WBC of $100/\mu\text{L}$ ($0.10 \times 10^9/\text{L}$), with 60% neutrophils, 28% lymphocytes, 11% monocytes, and 1% myelocytes. His CSF VDRL test result is negative. Urine cytomegalovirus (CMV) DNA testing is performed with negative results. The infant starts treatment with ampicillin and cefotaxime. His examination findings remain notable for decreased spontaneous movements, with no movement detected on his right side, qualitatively limited secondary to pain. The orthopedic subspecialist is consulted and radiography performed. Laboratory tests from both the mother and infant, combined with the radiographic and examination findings of the infant, confirm the diagnosis (Figs 1–3).

DISCUSSION

The admission prenatal testing of the mother shows significant findings of a rapid plasma reagin (RPR) titer of 1:64. The rest of her serologic tests, including

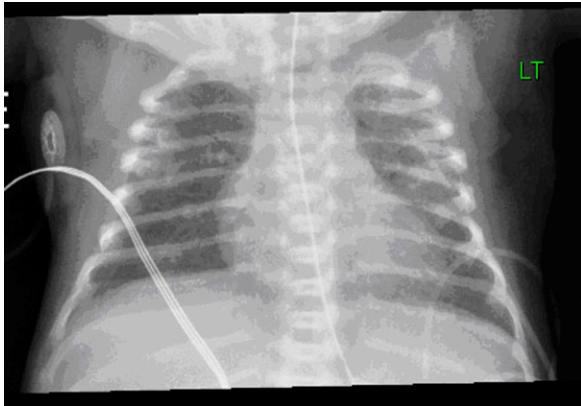


Figure 1. Chest radiograph of anteroposterior view demonstrating bilateral patchy opacities consistent with syphilitic pneumonitis.

human immunodeficiency virus, are unremarkable. Her urine toxicology test result is positive for cocaine. Laboratory testing of the infant showed an RPR titer of 1:64. His absence of a fourfold or greater titer is concerning for congenital syphilis (CS), and his abnormal physical examination findings confirm his diagnosis. Given these confirmatory findings, his antibiotic treatment is switched to intravenous penicillin G 50,000 U/kg per dose every 12 hours for 7 days, then 50,000 U/kg per dose every 8 hours for 3 days to complete a 10-day course in consultation with the infectious diseases specialist. Further recommendations include repeating the RPR titer every 2 to 3 months until the test is nonreactive or a fourfold decrease in titers is observed.

Chest radiography showed patchy opacities. The pediatric orthopedic specialist confirms the decreased spontaneous bilateral upper extremity movements, with the right extremities worse than the left. There is no appreciable pain with passive movement of the joints at the upper and lower extremities but subjective bony tenderness to the right and left humeri as well as bilateral femora and tibias. Official radiology reports showed periosteal reaction involving bilateral humeri and radii in the upper extremities, with a diffuse periosteal reaction, metaphyseal lucent zones, and irregular metaphyseal margins, with a sawtooth configuration consistent with the long bone changes seen in CS. Proximal left tibial metaphyseal lucencies were also observed, compatible with the Wimberger sign of CS. No fractures were seen in the radiographic images.

Acetaminophen is administered to the infant for pain management. Given his risk for pathologic fractures, the infant is handled gently and carefully, with physical therapy and occupational therapy advised after skeletal healing. Follow-up with the orthopedic physicians is arranged for monitoring of mild limb bowing.

Differential Diagnosis

Differential diagnosis of skeletal abnormalities includes the following:

- Battered-baby syndrome
- Subacute osteomyelitis
- Neonatal leukemia
- Neuroblastoma
- CMV infection
- Congenital rubella



Figure 2. Anteroposterior view on radiograph of right upper extremity showing diffuse periosteal reaction involving the humerus and metaphyseal lucencies at the proximal humerus.

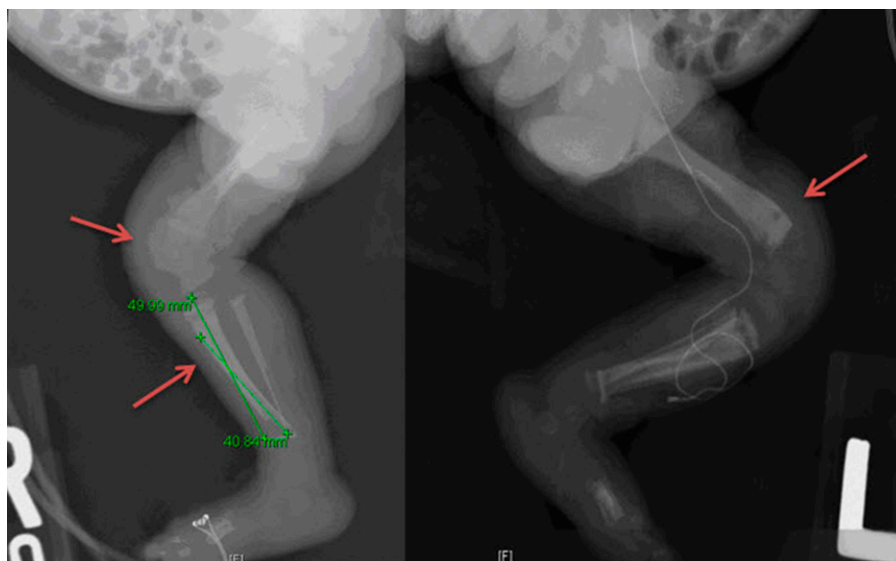


Figure 3. Anteroposterior view on radiograph of bilateral lower extremities demonstrating metaphyseal lucencies and periosteal reaction in the long bones of the right lower extremity.

Rickets

Neonatal hyperparathyroidism

The Condition

Infants with early CS most commonly present with evidence of transplacental transmission on serologic testing. Approximately two-thirds of diagnosed neonates are asymptomatic at birth. (1) Still, it remains important to recognize the various physical manifestations of CS, especially in mothers with inadequate prenatal care or with other risk factors, including living in areas of high syphilis prevalence, substance abuse, low socioeconomic status, or high-risk sexual behavior. (2) Early CS typically presents asymptotically within the first 4 to 8 weeks after birth. Clinical manifestations are varied and may be nonspecific. Findings include prematurity and/or low birthweight, hepatomegaly with or without splenomegaly, rash, rhinitis, and lymphadenopathy. CBC count findings may reveal anemia and/or thrombocytopenia. CSF values may show an elevated WBC count or protein count. (3) Although the classic “pneumonia alba” of CS on chest radiography is the opacification of both lung fields, diffuse infiltrates or nodularities are more commonly observed. (4)

Radiographic bony abnormalities are among the most commonly reported manifestations of early CS, reportedly seen in as many as 60% to 80% of symptomatic infants and 20% of asymptomatic infants. (5) Typically present at birth, these changes may occur within the first few weeks after birth. Classic bony involvement is bilateral, symmetric, polyostotic, and frequently involving the long bones.

Changes at the metaphysis include erosions, lucencies, or serrations. Classic signs include the Wimberger sign representing focal destruction of the medial aspect of the proximal tibial metaphyses and the Wegener sign representing serrations or a “sawtooth” appearance of the metaphysis. (6) Periostitis and osteitis may occur often with the presence of irregular new bone formation. (6) Other changes may include joint changes or swelling, pathologic fractures, and epiphyseal separation. Initially described by Parrot in 1871, infants may have pseudoparalysis or a limitation in movement secondary to pain. (7)

Management

Treatment regimens for early CS are recommended based on physical examination findings, serum nontreponemal titers (RPR or VDRL) of the infant, and adequate treatment of the mother. Treatment courses range from 1 to 10 days of parenteral (intravenous or intramuscular) penicillin G. Infants with positive serologic testing should undergo repeat testing every 2 to 3 months until a fourfold titer decrease is observed or the result is nonreactive. For infants whose titers fail to decline, repeat evaluation is recommended, including lumbar puncture with repeat antibiotic therapy. (8) In addition, infants with early CS should undergo serial eye and hearing examinations to detect latent signs of syphilis. Orthopedic specialists, physical therapists, and occupational therapists should be involved in care when bony abnormalities are detected. Gentle handling and pain control are significant factors in the appropriate care of skeletal manifestations.

Lessons for the Clinician

1. Although the clinical manifestations of CS are rarely seen in the developed world, it is important to recognize the signs and symptoms of early CS.
2. Physicians should continue to maintain high suspicion in cases of skeletal abnormalities, especially in the presence of other nonspecific symptoms and signs.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations and diagnostic features of perinatal infections with *Treponema pallidum*.
- Know the management and complications of perinatal infections with *Treponema pallidum*.

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Index of Suspicion in the Nursery

1 An Unusual Case of Neonatal Hyperthyroidism

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AUTHOR DISCLOSURE Drs Knight and Ejaz have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-day-old male infant presents to the endocrine clinic for evaluation of neonatal hyperthyroidism. The infant was born via a spontaneous vaginal delivery at 37 weeks' gestation to a gravida 1, para 1 mother. The infant's birthweight was 2,806.6 g. The pregnancy was significant for new-onset untreated hyperthyroidism in the mother diagnosed in the third trimester. She refused any intervention for her thyroid disorder.

Physical examination on day 13 after birth shows tachycardia, with a heart rate of 180 beats/min. Other vital signs are in the normal range. The infant is tolerating human milk well and has regained his birthweight. The parents report no feeding or sleeping issues; no tremors or jitteriness is noted. The infant has no palpable goiter. The mother appears to have a prominent goiter and reports a history of idiopathic tachycardia since infancy. Her laboratory findings are not available for review.

Newborn screening (on day 1) showed normal results on thyroid testing. Laboratory testing conducted on day 5 showed thyrotropin (TSH) of 7.5 mIU/L (neonatal range, 1.7-9.1 mIU/L), total thyroxine (T₄) of more than 30.0 µg/dL (386 nmol/L; neonatal range, 7.2-15.7 µg/dL [93-202 nmol/L]), free T₄ of 4.6 ng/dL (59 pmol/L; neonatal range, 0.9-2.3 ng/dL [12-30 pmol/L]), and triiodothyronine (T₃) of 256 ng/dL (3.94 nmol/L; neonatal range, 105-245 ng/dL [1.62-3.77 nmol/L]). Repeat blood test on day 9 showed TSH of 9.5 mIU/L and free T₄ of 4.1 ng/dL (53 pmol/L).

Because of the absence of clinical features of thyrotoxicosis, a decision was made not to start thionamides. Atenolol was started for isolated tachycardia. Isolated tachycardia in the infant and mother in the absence of other features of thyrotoxicosis pointed toward a genetic entity. Further testing confirmed the diagnosis.

DISCUSSION

Diagnosis

Neonatal hyperthyroidism is seen in 1 in 50,000 infants. Most of these cases are caused by transplacental passage of stimulatory immunoglobulins in mothers with Graves' disease. Neonatal Graves' disease is usually transient and can be confirmed by the presence of antibodies in the mother and infant. Other possibilities such as activating mutations of TSH receptor or inactivating mutations of thyroid hormone receptor should be considered in cases without the clinical features of thyrotoxicosis and with negative testing results for stimulatory immunoglobulins.

Repeat laboratory tests continued to show high T_4 with normal TSH. On day 24, TSH was 3.1 mIU/L, T_4 21.1 ng/dL (271 pmol/L), thyroid-binding globulin (TBG) 18 μ g/mL (307.7 nmol/L), and negative thyroid peroxidase, antithyroglobulin, thyroid-stimulating immunoglobulin (TSI), and thyroid-binding immunoglobulins (TBII). Absence of antibodies suggested a nonimmune cause for elevated free T_4 . Maternal laboratory tests showed a similar pattern, with TSH of 1.07 mIU/L, total T_4 15.5 μ g/dL (199.5 nmol/L), free T_4 2.7 ng/dL (34.7 pmol/L), T_3 229 ng/dL (3.53 nmol/L), TBG 18 μ g/mL (35 nmol/L), and negative thyroid peroxidase, antithyroglobulin, TSI, and TBII. Combination of normal TSH and high T_4 along with the absence of clinical features of thyrotoxicosis suggested a thyroid hormone receptor defect. Genetic testing confirmed a heterozygous mutation in the thyroid hormone receptor beta (*THRB*) gene *p.ALA317THR* in both the infant and mother. The mother was referred to genetic counseling to prevent any potential complications during her next pregnancy.

The Condition

Resistance to thyroid hormone usually presents with elevated serum levels of free thyroid hormone with nonsuppressed TSH, often with goiter and no clear clinical symptoms, and signs of thyrotoxicosis. The estimated prevalence of this disease is 1 in 40,000. More than 80% of cases occur because of mutations in the *THRB* gene. Recently, few cases of thyroid hormone receptor α (*THRA*) gene have been reported.

The *THRB* gene mutation presents in an autosomal dominant pattern. Mutations in the β subunit can result in impaired thyroid hormone signaling through decreased hormone binding to receptor, impaired interaction of thyroid receptor with required cofactors, or accelerated dissociation of hormone from the receptor and cofactor complex.

Three main types of resistance to thyroid hormone are seen. Generalized resistance to thyroid hormone is the most common type, and usually does not cause symptoms of thyrotoxicosis. Patients are asymptomatic because the resistance is balanced by increased production of thyroid hormone. Isolated symptoms of hyperthyroidism such as tachycardia and attention-deficit/hyperactivity disorder (ADHD) can be seen in these patients because of the predominance of the $THR-\alpha$ receptor in the cardiovascular system.

Patients with central resistance to thyroid hormone and peripheral resistance to thyroid hormone usually present with hyperthyroidism and hypothyroidism, respectively.

Treatment

Treatment is based on the symptoms exhibited by patients with generalized thyroid resistance. Patients with *THRB*

gene mutations usually present with isolated symptoms such as tachycardia and ADHD. Because these patients have a normal *THRA* gene, the excessive T_4 usually results in tachycardia. These patients should be treated with atenolol. Our patient and his mother also presented with only isolated tachycardia that was adequately controlled with low-dose atenolol. The patient may develop goiter and ADHD-like symptoms as he grows and thus requires close monitoring.

Genetic counseling is important for women with heterozygous mutation of the *THRB* gene. If a woman is pregnant with a child who does not carry the same mutation, the fetus can develop serious complications including miscarriage due to exposure to high thyroid hormone from the mother. The pregnant mother will require treatment in this case to prevent harmful effects on the fetus. However, if the fetus carries the same mutation as the mother, the mother will likely not require any thionamide treatment.

Lessons for the Clinician

- Although Graves' disease is the most common cause of neonatal hyperthyroidism, other entities such as thyroid-stimulating hormone (TSH) receptor and thyroid hormone receptor mutations should be considered in the absence of thyroid-stimulating immunoglobulin and thyroid-binding immunoglobulins.
- The combination of elevated free thyroxine along with normal TSH suggests resistance to thyroid hormone. These patients often require treatment for isolated tachycardia. Treatment with thionamides is not needed in these cases and may cause hypothyroidism if used.
- A pregnant woman with heterozygous mutation of the *THRB* gene should be offered genetic testing for her fetus during the first trimester. She may need treatment with thionamides if the fetus does not carry the same mutation.

American Board of Pediatrics Neonatal—Perinatal Content Specifications

- Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function
- Identify the etiology, clinical manifestations, laboratory features, and management of neonatal thyrotoxicosis

Suggested Reading

Dumitrescu AM, Refetoff S. The syndromes of reduced sensitivity to thyroid hormone. *Biochim Biophys Acta*. 2013;1830(7):3987–4003

Case 1: An Unusual Case of Neonatal Hyperthyroidism

Phillip Knight and Sehar Ejaz

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Index of Suspicion in the Nursery

3 An Unusual Case of Transient Neonatal Encephalopathy

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PRESENTATION

A 7-day-old female neonate presents to a local hospital with lethargy, grunting, fast breathing, and abnormal movements after a short history of poor feeding overnight. She was born at 39 weeks' gestation via cesarean section with a birthweight of 3,100 g to a 34-year-old woman. The parents are nonconsanguineous and the pregnancy was a result of in vitro fertilization with their own gametes. Antenatal screening and scans were normal. Cesarean section was performed because the labor did not progress; the neonate did not need any resuscitation. She nursed with the mother and went home breastfeeding on day 3 after birth. There is no family history of early neonatal deaths or neurologic dysfunction.

The neonate is brought to our tertiary neonatal center after stabilization with fluid bolus, broad-spectrum antibiotics, levetiracetam for suspected seizures, and mechanical ventilation. Initial differential diagnosis includes late-onset sepsis with meningitis and inborn error of metabolism with encephalopathy. Examination shows no dysmorphic features or neurocutaneous markers, and the head circumference is 32.6 cm. The infant is stuporous with paucity of spontaneous movements, depressed neonatal reflexes, and hypotonia. She is well perfused with normal heart sounds and femoral pulses and has no oxygen requirement. There is no pallor or jaundice and there is no organomegaly.

Arterial blood gas shows severe metabolic acidosis with pH of 7.15, P_{CO_2} 21 mm Hg (2.8 KPa), and bicarbonate 7.1 mEq/L (7.1 mmol/L). Normoglycemia is noted, with ongoing glucose infusion. Initial metabolic evaluation reveals hyperammonemia of 476 μ g/dL (340 μ mol/L) with mildly raised lactate at 36 mg/dL (4 mmol/L). Infection markers, blood counts, liver function tests, electrolytes, and creatinine concentration are within normal range. Enteral feeds are withheld, measures are taken to lower ammonia and prevent catabolism with oral sodium benzoate, parenteral nutrition with glucose infusion rate of 8 mg/kg per minute, and protein infusion of 0.25g/kg per day. Serial ammonia levels decline (at 4, 10, and 24 hours after admission, it is 434 μ g/dL [310 μ mol/L], 336 μ g/dL [240 μ mol/L], and 231 μ g/dL [165 μ mol/L], respectively) and normalize completely by 72 hours of admission. Brain ultrasonography shows cerebral edema and electroencephalography on day 2 of admission shows frontocentral and temporal epileptogenicity with normal background. Extended metabolic evaluation using tandem mass spectroscopy shows normal levels of plasma amino acids, acyl carnitine levels, and slightly low carnitine levels, making the diagnosis of organic acidemia, urea cycle defects, and defects

AUTHOR DISCLOSURES Drs Kumar, Athreya, Achuta, and Sundarraju have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

in fatty oxidation pathways less likely. Cerebrospinal fluid shows normal cell counts, biochemical profile, and lactate levels. Ammonia levels normalize, metabolic derangement resolves, and the infant's neurologic status returns to normal by day 7 of admission. She is taken off respiratory support. Gradual introduction of enteral feeds with breast milk does not result in any neurologic deterioration or rise in ammonia levels. Further evaluation shows normal urine orotic acid and cerebrospinal fluid α -amino adipic semialdehyde levels. Magnetic resonance imaging and magnetic resonance spectroscopy findings were normal, apart from a small infarct in the right caudothalamic groove. She has no clinical seizures but repeat electroencephalography a week later still shows some epileptogenicity and phenobarbital is added.

She is discharged from the hospital 2 weeks after admission. Because she presented in a metabolic crisis with transient hyperammonemia and encephalopathy with no diagnosis forthcoming from metabolic evaluation and brain imaging, genetic testing is carried out. Focused exome sequencing shows homozygous missense variant in carbonic anhydrase 5A (CA-VA) gene which is likely to be a pathogenic variant. Repeat carnitine measurements are normal. On follow-up she is thriving, remains neurologically normal, and is achieving her developmental milestones; her antiepileptic medications are being tapered.

DISCUSSION

Neonatal encephalopathy results from a wide variety of causes, among which hyperammonemia causing neonatal encephalopathy is considered to be an emergency requiring early identification and initiation of therapy. (1) Reaching an accurate diagnosis for the cause of hyperammonemia is often challenging and requires extensive investigation; often, even after extensive evaluation, the diagnosis may not be reached. Reversible conversion of carbon dioxide to bicarbonate is catalyzed by carbonic anhydrase (CA). Mitochondria are impermeable to bicarbonate, and 2 intramitochondrial carbonic anhydrases CA-VA and CA-VB are important in providing bicarbonate for multiple mitochondrial enzymes that catalyze the formation of essential metabolites of intermediary metabolism in the urea and Krebs cycles. (2)(3) CA-VA deficiency is an autosomal recessive inborn error of metabolism characterized clinically by acute onset of encephalopathy in infancy or early childhood. Biochemical evaluation shows multiple metabolic abnormalities, including metabolic acidosis and respiratory alkalosis. Other abnormalities

include hyperammonemia, hypoglycemia, increased serum lactate and alanine, and evidence of impaired provision of bicarbonate to essential mitochondrial enzymes. (4) Apart from episodic acute events in early childhood, the disorder shows a relatively benign course. Treatment with dextrose, bicarbonate, and carnitine provides clinical stability. Individuals may develop episodic acute metabolic decompensation during intercurrent illnesses. (4) CA-VA deficiency and long-term follow-up data have been sparsely reported in literature. Van Karnebeek et al reported 3 cases in 2 unrelated families. In 1 family, an affected girl showed mild axial hypotonia with average development, with below-average motor coordination at age 4.5 years, whereas her brother showed below-average psychomotor development at age 2.3 years. The third child showed normal psychomotor development at age 6 months. Diez-Fernandez et al described 10 more patients with CA-VA deficiency who were identified among a group of 96 patients with unexplained hyperammonemia, suggesting that this disease may be more common than rare forms of urea cycle disease such as N-acetylglutamate synthase deficiency. (5)

Lessons for the Clinician

- Neonatal encephalopathy with hyperammonemia warrants emergent treatment and efforts to establish underlying diagnosis.
- CA-VA deficiency is a differential diagnosis of early-onset life-threatening metabolic crisis, with hyperammonemia, hyperlactatemia, and ketonuria. This can be identified with focused exome sequencing and may be a more common cause of hyperammonemia than some rare metabolic errors. (5)
- CA-VA mutation will enable formulating sick day plans, genetic counseling, and screening of family members.
- Although metabolic derangement and encephalopathy may be transient, long-term neurodevelopment follow-up is indicated.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes, clinical features, laboratory evaluation, and acute management of metabolic encephalopathies in newborn infants

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Case 3: An Unusual Case of Transient Neonatal Encephalopathy
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Index of Suspicion in the Nursery

1 Apnea and Hypotonia in a 1-month-old Infant

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PRESENTATION

A 33-day-old male twin presents with apnea. He was delivered at 34.3 weeks by a 30-year-old gravida 6 para 4, aborta 1 woman with negative serologic findings. Her prenatal course was complicated by maternal urinary tract infection treated with antibiotics. The neonate was delivered vaginally at 34.3 weeks and required a 12-day stay in the NICU to establish feedings before being sent home. During the week leading up to apnea at home, he was found to have congestion, increased drooling, and decreased stools. He was feeding less and required syringe feedings. On the day of presentation he was found to have apnea requiring cardiopulmonary resuscitation. He was brought to the children's hospital emergency department. All other review of symptoms was negative.

In the emergency department, the infant is noted to have global hypotonia with weak cry, diminished suck, and grasp reflexes. The rest of the examination findings are normal. He has another episode of apnea and bradycardia requiring intubation and admission to the NICU. During his NICU stay, he remains globally hypotonic with no purposeful movements or reflexes.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for an infant with hypotonia is broad, including congenital myopathies, neuromuscular disease, metabolic disease, central nervous system disorders, connective tissue disease, and infection.

NICU COURSE

During his NICU stay, he remained globally hypotonic with no purposeful movements or reflexes. He received an extensive evaluation for hypotonia. An evaluation for infection, including respiratory viral panel, blood, urine, and cerebrospinal fluid culture, was negative. Antibiotics were discontinued after 48 hours given the negative cultures. Comprehensive metabolic panel and thyroid studies were all within normal range. Cerebrospinal fluid neurotransmitters were remarkable for low free γ -aminobutyric acid. Urine toxicology screen was positive for lidocaine. Imaging including computed tomography of the head and skeletal survey were all within normal limits. Brain and spine magnetic resonance imaging with spectroscopy was remarkable for symmetric increased T2 signal within the cord corresponding to lateral corticospinal tracts. Electroencephalography showed nonspecific encephalopathy with discontinuous immature pattern. Electromyography showed

NOTE The editors and staff of *NeoReviews* find themselves in the fortunate position of having too many submissions for the Index of Suspicion in the Nursery column. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will make an announcement in *NeoReviews* when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

AUTHOR DISCLOSURE Dr Castro has disclosed that she serves on the advisory boards of Biogen and Sarepta and receives research grants from Biogen, Sarepta, Reveragen, and Fibrogen. Drs Hoge, Thomas, Hanners, and Ali have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

global prolonged onset motor response and severely decreased amplitude and moderately decreased conduction velocity. Repetitive stimulation of nerves was unable to be completed because of minimal motor responses. Given the history of congestion, constipation followed by descending paralysis, and negative findings on evaluation, clinical suspicion for infant botulism became high, and it was arranged for the infant to receive infant botulism immunoglobulin (BabyBIG) before stool toxin test result was obtained. Within a week of receiving BabyBIG, the infant's tone markedly improved. He underwent extubation 1 week after the administration of BabyBIG and began tolerating full oral feeds. He was discharged from the hospital tolerating full feeds by mouth and with mild hypertonia that later spontaneously resolved in follow-up clinic. Stool toxin tests later had a positive result for botulinum toxin B and small amounts of botulinum toxin F.

INFANT BOTULISM

Infant botulism is a rare but life-threatening condition caused by a neurotoxin released from *Clostridium botulinum*, which is classified as a spore-forming, obligate anaerobic gram-positive bacillus. The neurotoxin inhibits the cholinergic neuromuscular junctions of striated and smooth muscles as well as tear, salivary, and sweat glands; this leads to symptoms of generalized weakness, constipation, and inability to tolerate secretions, often confused for upper respiratory symptoms in children. There are 8 different known botulism toxins, toxins A through H. Toxins A, B, E, and rarely, F, G, and H cause human disease. Toxin F is known to have a rapid onset, whereas the others have a more insidious onset. The toxins can be found in foods such as honey or canned items and dust or soil worldwide. The toxin can be acquired through eating contaminated foods, breathing contaminated dust, puncture wounds, or injection drugs with contaminated needles. To diagnose the disease, a high clinical suspicion is needed and the California Department of Health can be contacted for dispersion of BabyBIG. A stool sample should be sent for the toxin, but results take time, and treatment with BabyBIG should not be delayed if the clinical history fits with the signs of botulism. BabyBIG acquired from California does not include immunoglobulins against toxin F; therefore, if no improvement is seen with California's BabyBIG, the Centers for Disease Control and Prevention can be contacted to inquire for botulinum toxin F immunoglobulins with cases with a positive stool sample. A clinical response to the immunoglobulins should be seen within 1 week, with complete recovery seen within 2 to 3 weeks. This is in contrast to spontaneous resolution in a period of 6 weeks to months over the natural history of the disease if patients remain on

life-sustaining support, mainly respiratory support. BabyBIG therapy therefore can decrease morbidity, costs, and mortality.

Lessons for the Clinician

- Infantile weakness and hypotonia have a broad differential.
- Infantile botulism is rare, but given the correct clinical history and examination findings, it should be considered in the differential diagnosis.
- When a diagnosis of infantile botulism is made, BabyBIG therapy can save lives and costs.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress.
- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Know the epidemiology and pathogenesis of clostridial infections including *Clostridium botulinum*, *Clostridium difficile*, and *Clostridium tetani*.
- Know the prevention of clostridial infections including *Clostridium botulinum*, *Clostridium difficile*, and *Clostridium tetani*.
- Know the clinical manifestations, diagnostic features, management, and complications of clostridial infections including *Clostridium botulinum*, *Clostridium difficile*, and *Clostridium tetani*.
- Know the indications for and limitations of various neurodiagnostic tests.
- Know the significance of persistent neuromotor abnormalities in infancy (including asymmetries).
- Control of infection.

Suggested Readings

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Case 1: Apnea and Hypotonia in a 1-month-old Infant

Margaret "Katie" Hoge, Jennifer Muncy Thomas, Natasha Wyndham Hanners, Diana Patricia Castro and Noorjahan Ali

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Index of Suspicion in the Nursery

2 Asymmetrical Frontal Bossing and Refractory Seizures in a Newborn

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PRESENTATION

A male infant is born at 37 6/7 weeks' gestation by repeat cesarean delivery to a 33-year-old gravida 2, para 0 mother who had a previous fetal demise at 37 weeks' gestation (etiology unknown; no autopsy performed). For this current pregnancy the mother had regular prenatal care. Gestational diabetes was treated with dietary interventions. The mother is deaf due to childhood meningitis. She has a history of genital herpes simplex virus (HSV), with no active lesions at the time of delivery while receiving suppressive valacyclovir. The delivery is complicated by a nuchal cord and difficult extraction. The infant requires brief positive pressure ventilation. Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, are given. The infant weighs 3,735 g and is noted to have macrocephaly, with a head circumference of 15.8 in (40 cm). His length is 19.7 in (50 cm) and plots at 52%. He has a large open anterior fontanelle and asymmetrical frontal bossing, with prominence of the right forehead. The remainder of his newborn examination findings are normal. At 2 hours after birth he develops intermittent oxygen desaturations associated with arching of his back followed by right-sided shaking. His blood sugar level is 78 mg/dL (4.3 mmol/L). He is placed on 1-L nasal cannula oxygen and is loaded with 20 mg/kg of phenobarbital for suspected seizures. A blood culture is performed, and he is started on ampicillin, gentamicin, and acyclovir. A normal saline fluid bolus is given, and maintenance fluids are initiated at 80 mL/kg per day. The infant is then transferred to a facility that provides a higher level of care.

On arrival at our facility he is noted to be hypotonic and requires nasal cannula oxygen at 2 L. The results of his complete blood cell count and comprehensive metabolic panel are normal; rapid plasma reagin test is nonreactive; and surface HSV, urine, and blood cultures are negative. Lumbar puncture showed 9 white blood cells/ μL ($\times 10^9/\text{L}$), 10 red blood cells $\times 10^6/\mu\text{L}$ ($\times 10^{12}/\text{L}$), a protein level of 0.15 g/dL (1.5 g/L), a glucose level of 56 mg/dL (3.1 mmol/L), and Gram-stain/culture negative. Results of cerebrospinal fluid HSV polymerase chain reaction are negative. Computed tomographic scan shows right hemisphere hypertrophy that extends past midline, with hydrocephalus on the right and an unformed left lateral ventricle. Initial video electroencephalography the day after birth was abnormal, with tracé alternant pattern and sharp transients in all 4 quadrants, both excessive for age. There was no evidence of seizure activity.

AUTHOR DISCLOSURE Drs Frey, Hogden, and Berg have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

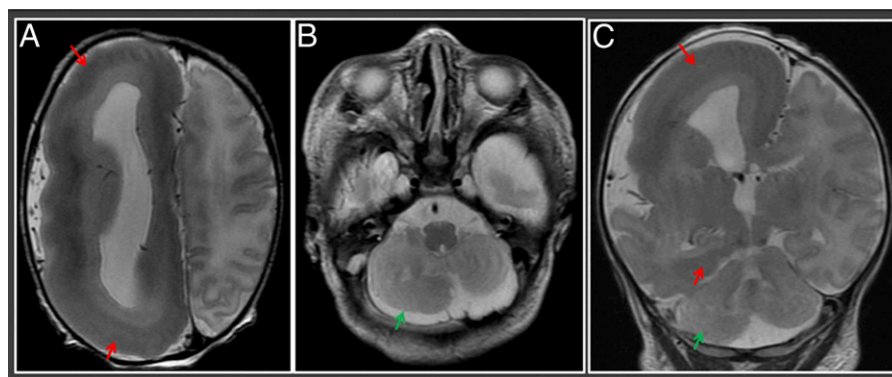


Figure. Axial (A) and coronal (C) T2-weighted magnetic resonance images demonstrate overgrowth of the right cerebral hemisphere with an enlarged, misshapen right lateral ventricle. There is absent sulcation in the right frontal and parietal lobes and reduced sulcation in the right temporal lobe. The cortex is markedly thickened (red arrows) in the right frontal and parietal lobes, as well as in the right medial temporal lobe. Axial T2 weighted image (B) demonstrates asymmetrically enlarged right cerebellar hemisphere (green arrow), also visualized in (C).

Further imaging includes a brain magnetic resonance image (MRI) (Fig) that reveals a diffusely abnormal right cerebral hemisphere, which is asymmetrically enlarged, with an enlarged, misshapen lateral ventricle consistent with hemimegalencephaly (HME). There is almost complete absence of sulcation involving the right frontal and right parietal lobes. There are rudimentary sulci present in the right temporal and right occipital lobes. The cortex is diffusely abnormal in appearance and thickened, with probable bandlike regions of gray matter heterotopia. Callosal dysgenesis is noted. There is asymmetry in the size of the cerebellar hemispheres, with the right being slightly larger than the left. The folia in the right cerebellar hemisphere also appear abnormal in the areas with thickening of the gray matter cortex.

By day 3 after birth the infant is off supplemental oxygen, is taking feeds orally, and has completed a 48-hour antibiotic/antiviral course after cultures were noted to be negative. That evening he develops abnormal eye movements and arm twitching, prompting an electroencephalography that demonstrates continuous high-voltage theta waves (~250–300 msec duration) in the right hemisphere that quickly generalized. The seizure continued for ~26 minutes, with a return to right hemispheric rhythmic activity for most of this time. After the initial prolonged seizure there was a period of ~4 hours without seizures, following which seizures recurred with a frequency consistent with status epilepticus, almost entirely in the right hemisphere. After the administration of multiple medication boluses (fosphenytoin, levetiracetam, lorazepam, midazolam, and phenobarbital), the frequency of seizures decreased and there was a period of ~9 hours with only a few brief seizures. Most of the seizures were without recognizable clinical changes.

However, the infant's status epilepticus recurs and proves refractory to multiple antiepileptic medications.

He receives additional boluses of levetiracetam, fosphenytoin, and phenobarbital and eventually a continuous infusion of midazolam. He develops respiratory depression and requires mechanical ventilation.

Based on the MRI findings and a Pediatric Neurology consultation, the infant is diagnosed as having HME. Given the inability to adequately control his seizure activity, consultation is made with an institution able to perform hemispherectomy for seizure control of a patient with HME. While preparing for transfer the infant develops metabolic acidosis, shock, and disseminated intravascular coagulation. The transfer is canceled due to the patient's instability. On day 11 after birth, due to continued worsening of his condition, the decision is made to redirect care to comfort measures. The infant is extubated and dies within minutes. The parents consent to a limited autopsy to obtain a brain biopsy for genetic testing. A somatic overgrowth gene set panel was performed, with no pathogenic or likely pathogenic variants identified.

DISCUSSION

The Condition

Hemimegalencephaly is a rare congenital malformation of the brain characterized by abnormal proliferation of part or all of 1 cerebral hemisphere with resultant extreme asymmetry. (1)(2) It is classified as a malformation attributed to abnormal neuronal and glial proliferation where anomalies of neural proliferation represent the primary event and alterations of neural cell migration occur secondarily. (1) (2) It is a rare condition reported in 1 to 3 of 1,000 epileptic children, with a mild prevalence in boys. (1) There are 3 types of HME. The first type, isolated HME, is the most common type, manifesting the typical brain findings but without

any cutaneous or systemic involvement. The second type, systemic HME, is associated with partial or total hemigigantism and/or certain neurocutaneous syndromes, including epidermal nevus syndrome, Proteus syndrome, Klippel-Trenaunay-Weber syndrome, hypomelanosis of Ito, and neurofibromatosis type 1. The third type, and most infrequent, is total HME in which in addition to the affected cerebral hemisphere there is enlargement of the ipsilateral cerebellum and brain stem. (1)(3)

Clinically, asymmetrical macrocrania is the main physical finding and may be the only sign noted at birth. Evidence of increased intracranial pressure is usually absent due to progressive adaptation of the fetal skull to the abnormal brain growth. Hemigigantism and classic skin findings are noted with the systemic varieties of HME. The classic neurologic triad seen in all forms of HME includes psychomotor retardation, contralateral motor deficit, and epilepsy. Seizures occur in more than 90% of affected individuals and are usually severe, progressive, and medication resistant. (1) Seizures usually begin during the first days after birth and are heterogeneous, including motor partial seizures, tonic and atonic seizures, spasms, myoclonic jerks, and early epileptic encephalopathy. Early resistance to antiepileptic drug therapy is the main characteristic of epilepsy in HME. (1)(3) A correlation between an earlier onset of epilepsy and the degree of severity of the motor deficit and intellectual level has been reported. (4)

The pathogenesis of HME is incompletely understood. Recent genetic studies implicate a somatic mutation in the cells of the affected hemisphere during early cerebral development. (3)(5)(6)(7)(8) De novo somatic mutations involving the *PIK3CA*, *AKT3*, and *MTOR* genes, which encode regulators of mechanistic target of rapamycin (mTOR) signaling, have been identified. (4)(5)(6)(7)(8) mTOR is a protein kinase that directs a signaling network that senses and integrates environmental cues to regulate cell division, growth, and survival. (8)(9) Gain-of-function mutations upregulate the mTOR pathway, altering neuronal growth and metabolism signaling. (3)(4)(7)(8)

Diagnosis

Fetal ultrasonography can raise suspicion for HME with identification of macrocephaly or ventricular asymmetry. However, MRI is the gold standard for diagnosis. (3) Almost all cases will demonstrate a malformed hemisphere with abnormal enlargement (mild to marked) and possible midline shift. The ipsilateral lateral ventricle is abnormal in size and shape. The cortical mantle is thick, with poor gray-white matter differentiation. The gyral architectural pattern

demonstrates areas of agyria, pachygyria, polymicrogyria, and lissencephaly that may alternate with areas of normal gyration. (1)(3)

Treatment

Most affected individuals will require multiple antiepileptic medications to control seizure activity. Frequent, refractory, intractable seizures may respond favorably to hemispherectomy. (3)(10) The goal of surgery is the complete resection or disconnection of epileptogenic zones, leaving the patient with less seizure burden and minimal postoperative neurologic deficits. Seizure control can be achieved in approximately 50% to 60% of patients with hemispherectomy, although most children will have persistent neurologic sequelae. (1)(10)

Anatomical hemispherectomy is associated with the highest rate of postoperative seizure control. Bleeding complications are significant with this procedure. (1) Functional hemispherectomy with disruption of the connecting nerves and tissues while leaving the hemisphere in place is an alternative. (1)

Improvement of either the motor function level or intellectual development was seen in most patients after functional hemispherectomy in a survey of Japanese patients with HME. Early surgical intervention (reported in patients as young as 3 months) is recommended for the early-onset epilepsy group to preserve psychomotor development. (1)(4)

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the familial/genetic features of neurologic disorders associated with increased head circumference.
- Understand the differential diagnosis and evaluation of neonatal seizures.

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Case 2: Asymmetrical Frontal Bossing and Refractory Seizures in a Newborn

Teresa Frey, Laurie Hogden and Aaron Berg

NeoReviews 2019;20:e41

DOI: 10.1542/neo.20-1-e41

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Index of Suspicion in the Nursery

2 Beware of Lumps and Bumps after Cooling!

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AUTHOR DISCLOSURE Drs Vali and Lakshminrusimha have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

The infant is born to a 31-year-old primigravida mother by cesarean delivery due to nonreassuring fetal heart rate and chorioamnionitis. Rupture of membranes is prolonged at 47 hours with meconium-stained amniotic fluid.

At birth, the newborn is noted to have poor tone and respiratory effort. He undergoes intubation and is admitted to the NICU for further observation and management. Apgar scores are 2, 5, and 7 at 1, 5, and 10 minutes, respectively. Arterial cord gas has a pH of 6.8 and a base deficit of 24 mEq/L (24 mmol/L).

The patient demonstrates signs and symptoms of moderate hypoxic-ischemic encephalopathy and meets the criteria for whole body hypothermia therapy. He is started on parental nutrition. He has evidence of pulmonary hypertension on echocardiography and requires inhaled nitric oxide for 2 days while undergoing hypothermia treatment. He maintains adequate blood pressures and does not have any hemodynamic decompensation. He receives 2 doses of fresh frozen plasma to correct laboratory indices that demonstrate abnormal coagulation profiles. Following rewarming and after obtaining a brain magnetic resonance imaging scan (which is unremarkable) he undergoes successful extubation on the 4th postnatal day. His respiratory support is gradually weaned and he remains in room air from day 6 of age onwards. He is slowly introduced to enteral feeds and reaches full oral feeds by 9 days of age. His neurologic examination findings are normal.

Erythematous, indurated plaques are noted over the upper back, shoulders, and back of the head on the 10th day consistent with a diagnosis of subcutaneous fat necrosis (SCFN). During the NICU admission, his total calcium levels remain within normal range (Fig 1A). The patient's ionized calcium the day before his discharge is 5.4 mg/dL (1.3 mmol/L; normal range 4.5–6.2 mg/dL [1.1–1.55 mmol/L]). On the day of discharge, the ionized calcium is 6.0 mg/dL (1.5 mmol/L) and the patient receives a dose of intravenous (IV) furosemide. The plan at discharge is for the pediatrician to follow up the calcium weekly until the SCFN resolves.

DISCUSSION

Diagnosis

The first outpatient calcium follow-up blood sample cannot be evaluated because the sample quantity was deemed insufficient. A few days later, a repeat sample was obtained and reported at 19.8 mg/dL (4.9 mmol/L; approximately

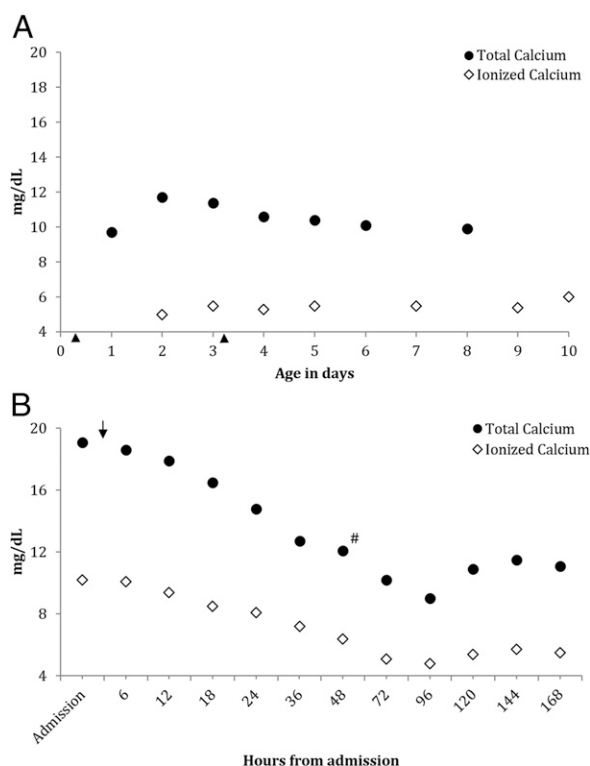


Figure 1. A. Total and ionized calcium levels during NICU admission. Arrowheads indicate period of whole body hypothermia. B. Total and ionized calcium levels during readmission. Arrow indicates initiation of intravenous (IV) maintenance fluids, IV furosemide, and methylprednisolone. # represents cessation of IV fluids and medications, and initiation of prednisolone until discharge.

2 weeks from discharge). The patient was instructed to present to the children's hospital emergency department (ED) immediately. He remains asymptomatic with no signs or symptoms of hypercalcemia.

The Condition

SCFN is an uncommon condition, usually observed in a minority of newborn infants with a history of hypoxic-ischemic encephalopathy treated with therapeutic hypothermia.

Following 3 large randomized controlled trials, in newborns with hypoxic-ischemic encephalopathy, therapeutic moderate hypothermia has become the standard of care and is being increasingly implemented in NICUs. The original trials were not powered to detect rare adverse events and the recognition that moderate hypothermia increases the risk of SCFN has become more widespread with rising cases. Currently, the incidence of SCFN is estimated around 1% to 3%.

SCFN is characterized by erythematous, firm, indurated, nonpitting plaques or nodules over the back, buttocks, thighs, posterolateral surface of the forearms, and

rarely, involving the face. Although the exact pathophysiology remains unknown, hypothermia can further compromise skin perfusion in the asphyxiated newborn, exacerbating ischemic injury to immature fat cells that can result in necrosis and solidification. SCFN is usually a self-limiting disorder of adipose tissue presenting in the first week after birth and resolving by 6 months of age.

The associated complication of hypercalcemia, reported in up to 80% of SCFN cases (sometimes presenting with critically elevated calcium levels as observed in the current patient), requires aggressive treatment. This makes the recognition of SCFN by the parents and pediatrician imperative to the well-being of the newborn. A widely accepted hypothesis explaining the development of hypercalcemia in SCFN is that the release of 1,25-dihydroxy vitamin D during necrosis of granulomatous fat cells results in increased intestinal calcium absorption.

SCFN can be distinguished from sclerema neonatorum (SN), also a disorder of fat necrosis, by the presentation of SCFN as circumscribed lesions that are mobile and self-limited; SN, however, is generalized and characterized by hardening of the skin that gets bound down to the muscle and bone. SN hinders breathing and movement in the neonate, and is associated with a high incidence of fatality.

Treatment

Given the overall rare occurrence of SCFN, and even less frequent associated severe complications, the potentially serious adverse effects of hypercalcemia may be underappreciated by caregivers. In the ED, the patient in the current case was aggressively fluid resuscitated and admitted to the PICU for possible dialysis. He received maintenance IV fluids, IV furosemide, and methylprednisolone for 2 days. He did not have any signs of arrhythmia and did not require dialysis. With improving calcium levels, he was transferred to the inpatient floor for further management and observation. He received 1 dose of IV pamidronate with only a transient effect and therefore continued to take oral steroids until his calcium levels normalized before discharge from the hospital (Fig 1B).

In symptomatic patients, treatment relies on low-calcium and low-vitamin D diets, IV hydration and loop diuretics, corticosteroids, and bisphosphonates with the possible need for dialysis.

Lessons for the Clinician

Because there are currently no guidelines for pediatricians on how best to manage newborns at risk for SCFN, we propose the following recommendations:

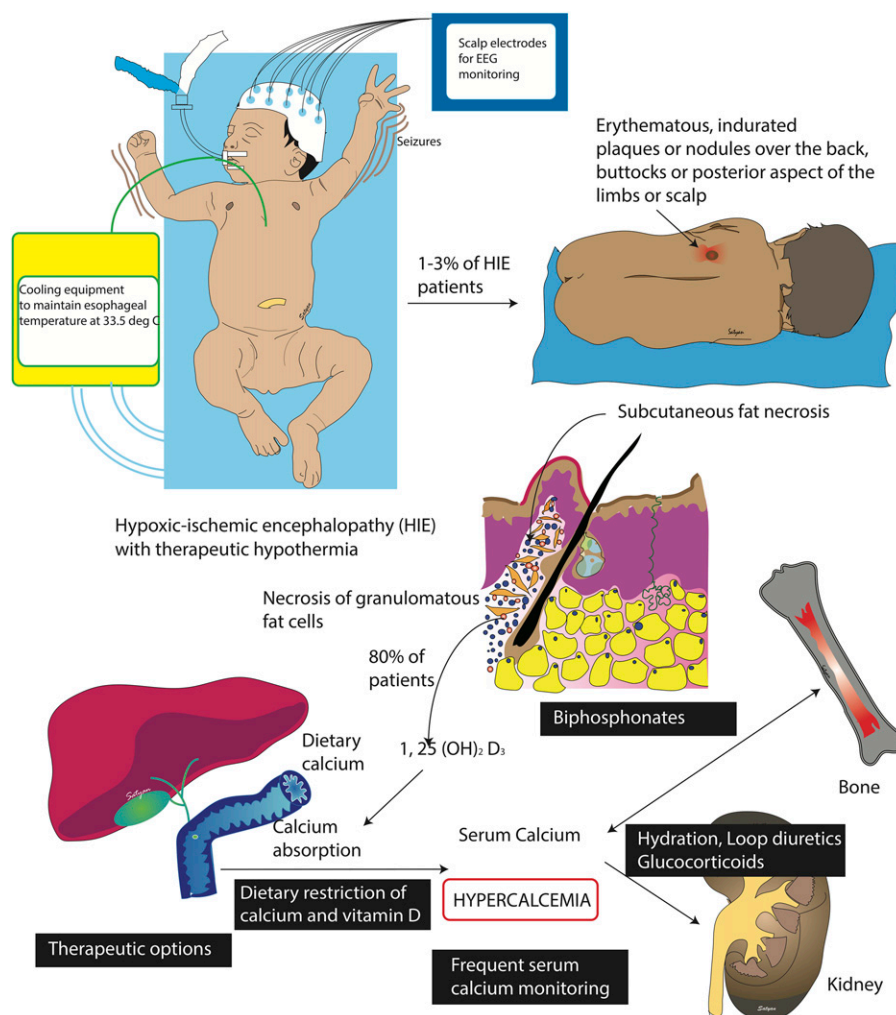


Figure 2. Infographic showing the pathophysiology and management of hypercalcemia in neonatal subcutaneous fat necrosis. Hypoxic-ischemic encephalopathy and therapeutic hypothermia can increase the risk of subcutaneous fat necrosis in newborn infants. Necrosis of fat cells is thought to release active vitamin D, which leads to increased absorption of calcium and hypercalcemia. Management (shown in black boxes) includes limiting calcium and vitamin D intake and promoting excretion of calcium.

- In the event that the newborn shows signs of SCFN during the hospitalization, neonatal care clinicians should document normal calcium levels before discharge.
- Calcium levels should be routinely followed on an out-patient basis, and vitamin D supplementation deferred, until nodules have resolved.
- In newborns who do not show any signs of SCFN at discharge, parents should be instructed to notify pediatricians if they notice any redness or firmness on their child's skin.
- Pediatricians are encouraged to be diligent in their examination, particularly when examining the newborn's skin to make sure developing SCFN is not missed.

By increasing parental and pediatrician awareness of the rare, albeit serious, complications of SCFN with the help of this infographic (Fig 2) we hope to limit cases of hypercalcemia associated with SCFN.

Acknowledgment

This study was funded by National Institute of Child Health and Human Development grants RO1HD072929 and UG1HD068263 (S.L.).

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology and clinical manifestations of neonatal hypercalcemia.
- Know the laboratory features and approach to therapy of neonatal hypercalcemia.

Suggested Readings

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Case 2: Beware of Lumps and Bumps after Cooling!

Payam Vali and Satyan Lakshminrusimha

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Index of Suspicion in the Nursery

1 Bilious Vomiting in a Term Neonate

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PRESENTATION

A 2.34-kg male infant is born to a gravida 3 woman with 2 previous abortions at 37.1 weeks of gestation. A cesarean delivery is performed because of fetal distress with oligohydramnios and abnormal Doppler ultrasonography findings. The antenatal period is largely uneventful, with second-trimester antenatal anatomy ultrasound scan reported as normal. However, fetal growth is noted to be poor (lag of 2 weeks) on antenatal ultrasonography at 34 weeks and abnormal Doppler findings are reported at 37 weeks. The neonate does not require any active resuscitation at birth and is transferred to the NICU for low-birthweight care. Intravenous fluids are started initially in view of abnormal antenatal Doppler ultrasonography findings and feedings are introduced at around 21 hours after birth. First meconium is passed at 6 hours of age. The neonate, however, develops



Figure 1. Supine radiograph suggesting the presence of a large cystic structure in the right iliac fossa.

AUTHOR DISCLOSURE Drs Goel, Mittal, and Arora have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

feeding intolerance in the form of bilious vomiting and abdominal distention on the second day. Sepsis screening result is negative (total white blood cell count: $7,500/\mu\text{L}$ [$7.5 \times 10^9/\text{L}$]; absolute neutrophil count: $2,850/\mu\text{L}$ [$2.85 \times 10^9/\text{L}$]; C-reactive protein: 0.1 mg/dL [9.5 nmol/L]; platelet count: $230 \times 10^3/\mu\text{L}$ [$230 \times 10^9/\text{L}$]; peripheral smear: no toxic granules).

In view of the bilious vomiting, volvulus, malrotation, and intestinal obstruction are included in the differential

diagnosis and abdominal radiography is ordered. Supine radiography (Fig 1) suggests the presence of a large cystic structure in the right iliac fossa, which persists on serial radiography. Pediatric surgery consultation is sought and a conservative approach is advised. The neonate is now kept nil per os (nothing by mouth) with the addition of a prokinetic agent (domperidone). Feedings are reintroduced after 24 hours (day 3 after birth) but it again leads to bilious vomiting; repeat radiography suggests persistence of the same cystic

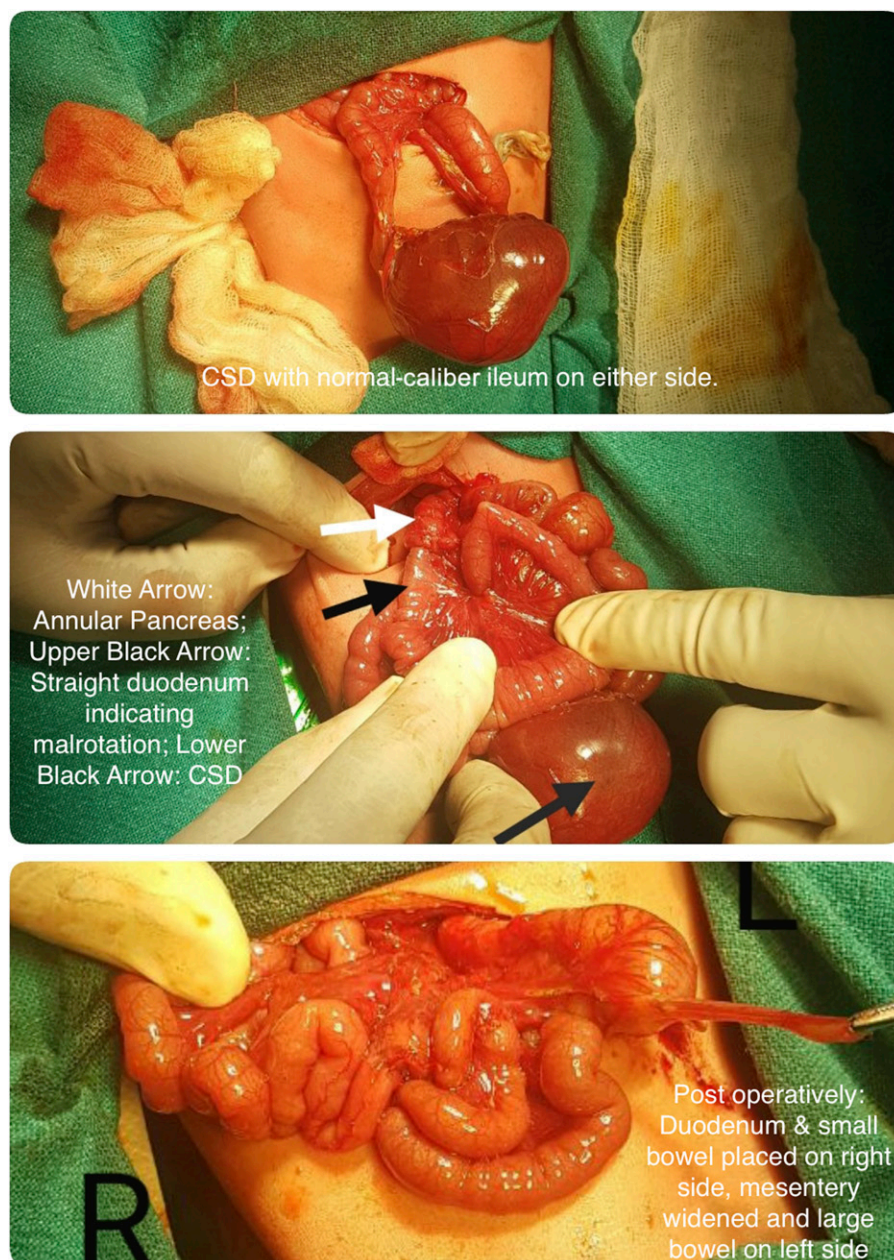


Figure 2. Congenital segmental dilation (CSD) with normal-caliber ileum on either side. White arrow shows annular pancreas; upper black arrow, straight duodenum indicating malrotation; lower black arrow, CSD.

shadow in the right iliac fossa. Exploratory laparotomy is planned for the neonate on the 4th day after birth.

Laparotomy reveals cystic dilation of the ileum with malrotation, along with an incidental finding of an asymptomatic annular pancreas. The dilated ileal segment is 5×4 cm in size with continuation of normal ileum on either side of the dilated segment (Fig 2). Because the primary pathology is cystic dilation of ileum, which is causing intestinal obstruction, resection of the dilated bowel along with end-to-end ileal anastomosis is performed. Malrotation can cause problems later on, so the Ladd procedure is performed, which includes surgical division of the Ladd band and widening of small intestine mesentery (Fig 2). An appendectomy is also performed at the same time, followed by reorientation of the small bowel on the right side and caecum and colon on the left side. Annular pancreas is left intact because it is not found to be causing any duodenal obstruction. Histopathology (Fig 3) shows all layers of intestine with normal intestinal mucosa and without any heterotopic tissue, consistent with the diagnosis of congenital segmental dilation (CSD) of the ileum.

DISCUSSION

The Condition

Also known as “segmental dilation of the ileum,” CSD is a dilated full-thickness segment of the ileum with normal-caliber ileum on either side. It is a rare condition of unknown etiology with about half of the cases presenting in the neonatal period. (1) CSD is characterized by the Swenson and Rathauser criteria as: 1) limited bowel dilation with a 3- to 4-fold increase in caliber, 2) an abrupt transition between dilated and normal bowel, 3) no internal/external barrier distal to the dilation, 4) a clinical picture of intestinal obstruction (complete or partial) 5) a normal neuronal plexus, and 6) complete recovery after

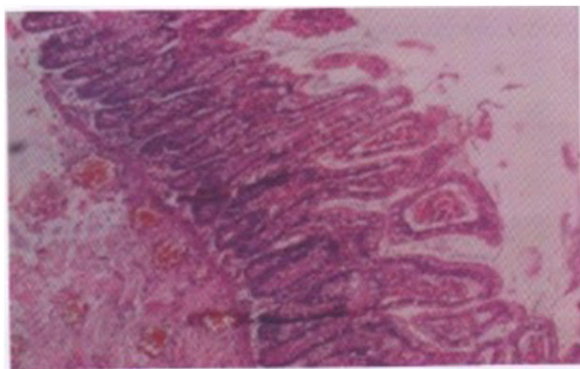


Figure 3. Histopathologic findings in all layers of intestine with normal intestinal mucosa and without any heterotopic tissue.

resection of affected segment. (2) The cause of CSD remains unknown. Postulated mechanisms include surrounding structures such as vitelline vessels and omphaloenteric bands compressing on the bowel loops at both ends, leading to focal segmental dilation without altering the bowel histology. (3)

It can present as an isolated entity or can be associated with other congenital malformations as seen in the current case, where it was associated with malrotation. To our knowledge, this is the first case in the literature in which CSD coexisted with asymptomatic annular pancreas. The clinical presentation is generally nonspecific, with the affected neonate developing features of bowel obstruction in the form of abdominal distention and bilious vomiting. Differential diagnoses include malrotation, volvulus, and intestinal obstruction because of other causes. Constipation can sometimes be associated, in which case Hirschsprung disease also becomes a possibility in the differential diagnosis.

Diagnosis

Antenatal ultrasonography can sometimes suggest a dilated bowel loop. Waters et al (4) and Paradiso et al (5) described the antenatal ultrasonographic features associated with CSD. In the current case though, antenatal ultrasonography findings were reported as normal. Postnatal diagnosis requires a high index of suspicion but the diagnosis is usually made only during exploratory laparotomy performed for clinical intestinal obstruction. Supine and erect radiography suggests a dilated loop of bowel in right iliac fossa (as seen in the current case) with or without air fluid levels but with an otherwise normal gas pattern in the rest of the bowel. (6) Rarely, barium enema studies are also ordered but usually reveal findings similar to those seen on plain radiography.

Treatment and Prognosis

Definitive treatment is resection of the dilated segment, followed by end-to-end anastomosis of the pre- (proximal) and post- (distal) ends. Prognosis is usually excellent after surgical resection. In the current case also, the surgery was well tolerated and the infant remained stable in the postoperative period. He continued to receive parenteral nutrition support for the next 3 days, after which feedings were initiated and gradually increased as tolerated. Full feedings were reached on the 10th postoperative day. The infant was discharged from the hospital on day 18 after birth, breast-feeding and doing well on follow-up and gaining adequate weight.

Lessons for the Clinician

- A high index of suspicion is required for considering a diagnosis of CSD in a neonate with features of intestinal obstruction.
- Radiography is suggestive but not diagnostic, which is usually confirmed during laparotomy performed for intestinal obstruction.
- Prognosis is usually excellent after surgical resection of the dilated segment and end-to-end anastomosis of the normal-caliber ileum.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the morphogenesis of the GI tract and factors that lead to congenital malformations.

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Case 1: Bilious Vomiting in a Term Neonate

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Index of Suspicion in the Nursery

1 Bluish Discoloration in an Infant

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AUTHOR DISCLOSURE Drs Singh, Kler, and Thakur have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term male infant presents to the NICU 19 days after birth with bluish discoloration of the body of 4 days' duration. He is delivered vaginally by a 28-year-old gravida 2 mother at 39 weeks of gestation. The infant is the product of a nonconsanguineous marriage. There are no antenatal complications. His birth-weight, length, and occipitofrontal circumference are 3,700 g, 52 cm, and 34.5 cm (50th percentile), respectively, on the Fenton growth chart. The infant cried immediately after birth and did not require any resuscitation. He is breastfeeding soon after birth and is discharged 48 hours after delivery. At home, he is started on formula feeding 5 days after delivery. On day 15 after birth, the parents noticed bluish discoloration of the body (Fig), but the infant has no difficulty breathing. He is brought to the hospital 19 days after birth. At the time of admission, his temperature is 98.2°F (36.8°C), heart rate is 160 beats/min, respiratory rate is 52 breaths/min, and pulse oximetry shows saturation of 80%. On cardiovascular examination, heart sounds are normal and there is no murmur. Pulses are felt with equal strength in all 4 limbs. Mean arterial pressure is 52 mm Hg and there is no discrepancy in blood pressure in upper and lower limbs. Saturation is 85% even on fractional inspired oxygen (FiO₂) concentration of 1.0. Blood glucose level measured with a chemically treated paper stick (Dextrostix) was 68 mg/dL (3.7 mmol/L). Arterial blood gases are as follows: Fio₂, 1.0; pH, 7.41; partial pressure of carbon dioxide (Paco₂), 38 mm Hg (5.0 kPa); partial pressure of oxygen, 176 mm Hg (23.4 kPa); bicarbonate, 23 mEq/L (23 mmol/L); oxygen saturation (Sao₂), 100%; and base excess, -2 mmol/L.

DISCUSSION

Diagnosis

Chest radiography shows normal cardiac shadow and lung fields. Echocardiography reveals normal structure and function of the heart. On venipuncture, the blood appears chocolate brown. Investigations for sepsis, complete blood cell count, C-reactive protein, and blood cultures are all normal.

Because of the saturation gap between this infant's pulse oximetry saturation (SpO₂=85%, FiO₂=1.0) and the calculated blood gas SaO₂ (SaO₂=100%, FiO₂=1.0) and a normal arterial partial pressure of oxygen (PaO₂=176 mm Hg, FiO₂=1.0), a serum methemoglobin (Met-Hb) level measurement is taken, which is 57%. There is no family history of methemoglobinemia, and Met-Hb



Figure. Bluish discoloration in an infant.

levels of both parents are normal. On further history, it is revealed that the infant was given formula mixed with well water. Laboratory testing of the water sample found the nitrate content to be 27 parts per million (ppm) compared with a normal level of less than 10 ppm.

Hemoglobin electrophoresis did not reveal the presence of hemoglobin M (Hb A 46.4%, A₂ 0.9%, and F 49.2%), which could be an important cause of methemoglobinemia. Renal function tests including electrolytes and liver function tests are normal.

Condition

Methemoglobinemia is a condition in which the Met-Hb level in blood is higher than 1%. In Met-Hb, iron is in the ferric rather than the ferrous form, which leads to an inability of red blood cells to carry oxygen. In the presence of Met-Hb, the remaining ferrous iron in hemoglobin binds oxygen with greater affinity, thereby shifting the oxygen hemoglobin dissociation curve to the left. This results in decreased oxygen delivery to the tissues, leading to hypoxia and acidosis. Clinical symptoms are proportional to the level of Met-Hb in the blood. Clinical symptoms include cyanosis, breathing difficulty, and decreased activity. Levels between 50% and 70% can result in severe acidosis, abnormal cardiac rhythm, seizures, and coma. Methemoglobin level above 70% is usually fatal. (1) Generally Met-Hb levels less than 15% do not cause any symptoms but in the case of anemia, sepsis, acidosis, cardiovascular compromise, and presence of other abnormal hemoglobins, the symptoms may get more pronounced even at much lower levels.

Methemoglobinemia in the newborn may have either congenital or acquired causes. Congenital causes leading to methemoglobinemia are rarer than causes of environmental toxicity. Spontaneously formed Met-Hb is less than 1% of total hemoglobin and is reduced to normal

hemoglobin by protective antioxidant enzyme system, namely nicotinamide adenine dinucleotide (NADH) Met-Hb reductase (cytochrome b₅ reductase), nicotinamide adenine dinucleotide phosphate (NADPH) Met-Hb reductase, and to a lesser extent, the ascorbic acid and glutathione enzyme systems. NADH-dependent pathway is the major enzymatic system responsible for the removal of 95% to 99% of Met-Hb that is produced under normal circumstances. (2) Congenital causes include deficiency of cytochrome b₅ reductase enzyme. Congenital methemoglobinemia due to cytochrome b₅ reductase has been divided into 2 types. In type 1, red blood cells lack the enzyme, whereas in type 2, the enzyme is deficient in all cells of the body. Infants with type 1 only have cyanosis whereas type 2 is seen with developmental delay, intellectual disability, failure to thrive, and seizures. All of these are inherited as autosomal recessive disorders. Another cause of congenital methemoglobinemia is hemoglobin M, which includes structural change in the α and β chain that stabilizes the hemoglobin in the ferric state. (2) Hemoglobin M disease due to α chain variant presents with cyanosis at birth whereas the β chain variant presents after 4 to 6 months of age. It is inherited as an autosomal dominant disorder.

The acquired form of methemoglobinemia occurs because of the increased oxidative stress on red blood cells. Oxidative stress could be drugs, chemicals, or toxins. Drugs causing methemoglobinemia include local anesthetics, inhaled nitric oxide, antimalarials, sulphonamides, dapsone, and nitroglycerine. Environmental toxins and chemicals include nitrates, chlorates, copper sulfate, aniline dyes, naphthalene, and some insecticides. Nitrates and nitrites are responsible for a large proportion of intoxication-induced methemoglobinemia. Nitrates can be present in preservatives and dyes used in the food industry, in industrialized infant foods, and also in contaminated drinking water. (3)(4) Cases of methemoglobinemia have been reported in areas with water containing a high concentration of nitrates. (5) Premature infants and those younger than 4 months are more predisposed to acquired forms of methemoglobinemia because of the predominance of fetal hemoglobin, decreased activity of NADH reductase, and higher gastric pH in infants. In these infants, fetal hemoglobin is present in higher proportion of total hemoglobin and is more susceptible to Met-Hb formation by oxidizing agents. Further newborns have lower activity of NADH-dependent reductase to counteract the oxidative stress and spontaneously formed Met-Hb. In neonates, the level of enzyme is 60% of the normal adult value. Finally, the gastric pH is higher than in children and adults and resultant higher acidity favors bacterial growth, which converts nitrates to toxic nitrites.

Arterial blood in the condition is chocolate brown rather than bright red. In a case of suspected methemoglobinemia, co-oximetry panel should be sought in arterial blood gas analysis, which can measure dyshemoglobins such as Met-Hb and carboxyhemoglobin other than oxyhemoglobin and deoxyhemoglobin. Newer pulse oximeters using multiwavelength technology can also reflect Met-Hb levels.

In severe methemoglobinemia, evaluation for end-organ dysfunction should be done in the form of liver and kidney function tests. Neuroimaging is needed in the presence of neurologic symptoms. Specific enzyme assay needs to be conducted if hereditary methemoglobinemia is suspected.

Treatment

The infant described was treated with oral methylene blue (2 mg/kg) and his serum Met-Hb level dropped to 4.6% and 2.1% after 6 hours and 16 hours, respectively. His extremities turned pink, and he started accepting breast feeds well. The infant's glucose-6-phosphate dehydrogenase (G6PD) levels were evaluated before he was given methylene blue and found to be normal.

Treatment of methemoglobinemia involves methylene blue, which in the presence of NADPH, is converted to leucomethylene blue, which results in nonenzymatic reduction of Met-Hb. Methylene blue is contraindicated in case of G6PD deficiency and is ineffective when the methemoglobinemia is due to hemoglobin M. Methylene blue itself is an oxidant, and the total dose should not exceed 7 mg/kg. It can be given in either an injectable or oral form. Vitamin C directly reduces Met-Hb, but the rate of the reaction is too slow for it to be effective when used alone. Other options are hyperbaric oxygen and exchange transfusion in cases in which methylene blue is either contraindicated or ineffective. (6)(7)

Progression

The mother was counseled about breastfeeding, and the infant was exclusively breastfeeding at the time of discharge. The infant was discharged in stable condition, and the parents were advised to use packaged mineral water for formula preparation if needed. There was no recurrence of cyanosis and the infant remained well.

Infants with acquired methemoglobinemia respond very well once the responsible drugs, chemicals, or toxins

are identified and avoided. Infants with type 1 methemoglobinemia usually remain well whereas those with type 2 methemoglobinemia generally die within the first few years after birth.

Lessons for the Clinician

- Neonatal methemoglobinemia is a rare but treatable cause of cyanosis without respiratory distress.
- Patients who develop acquired methemoglobinemia secondary to toxin exposure should be advised to avoid exposure to potential oxidative stress. Environmental toxins should be identified and reexposure should be avoided.
- Methemoglobinemia can be life-threatening. Early recognition is mandatory to prevent unnecessary investigations and delay in management.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Formulate a differential diagnosis for a cyanotic neonate.

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Index of Suspicion in the Nursery

3 Bradycardia in a Vigorous Newborn

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PRESENTATION

A female infant is delivered at 38 weeks and 3 days to a 32-year-old gravida 2, para 1 woman via a low transverse cesarean section. At delivery, the neonate is noted to have a spontaneous cry, appropriate respiratory effort, and active movement of all extremities; however, her initial heart rate is noted to be 40 beats/min.

After drying and stimulation, her oxygen saturation on pulse oximetry is noted to remain at 60% at 3 minutes after birth. Blow-by oxygen is started. Despite this intervention, she develops nasal flaring and subcostal retractions. Facial continuous positive airway pressure (CPAP) is initiated with positive end-expiratory pressure of 5 mm Hg and then the infant is transitioned to nasal CPAP. Oxygen concentration is titrated to 100% and oxygen saturations on pulse oximetry increase to greater than 90%. Her work of breathing normalizes. Apgar scores are noted to be 6 and 8 at 1 and 5 minutes, respectively.

Despite effective ventilation and oxygen saturations, the infant's heart rate remains between 40 and 50 beats/min. A 12-lead electrocardiogram is obtained, which confirms the diagnosis (Fig 1).

DISCUSSION

Diagnosis

This infant's presentation was concerning for a cardiac anomaly, given the intractable bradycardia despite adequate respiratory support, and oxygen saturations. Electrocardiographic findings were consistent with complete heart block (congenital atrioventricular block, third degree). She began receiving an isoproterenol infusion starting at 0.15 µg/kg per minute to increase ventricular rate.

On day 1 after birth, isoproterenol was discontinued to obtain baseline hemodynamics and heart rate, which remained at approximately 40 beats/min. Her systolic blood pressures averaged between 60 and 70 mm Hg and her diastolic blood pressures averaged between 25 and 35 mm Hg.

By day 2 after birth, she was transferred to the pediatric cardiac intensive care unit; the pediatric cardiothoracic surgeon carried out a minimally invasive placement of a single right ventricular epicardial bipolar pacing lead and generator using a subxiphoid approach. The pacemaker mode was VVI at a rate of 80 beats/min. Her remaining hospital course was uneventful and she was discharged from the hospital with her family on day 5 after birth.

Maternal and antenatal history was significant for maternal autoimmune arthritis with antibody positivity for anti-SSA/Ro and anti-SSB/La antibodies.

AUTHOR DISCLOSURE Drs Timothy, Stetson, Qureshi, Wilkins, and Asay have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

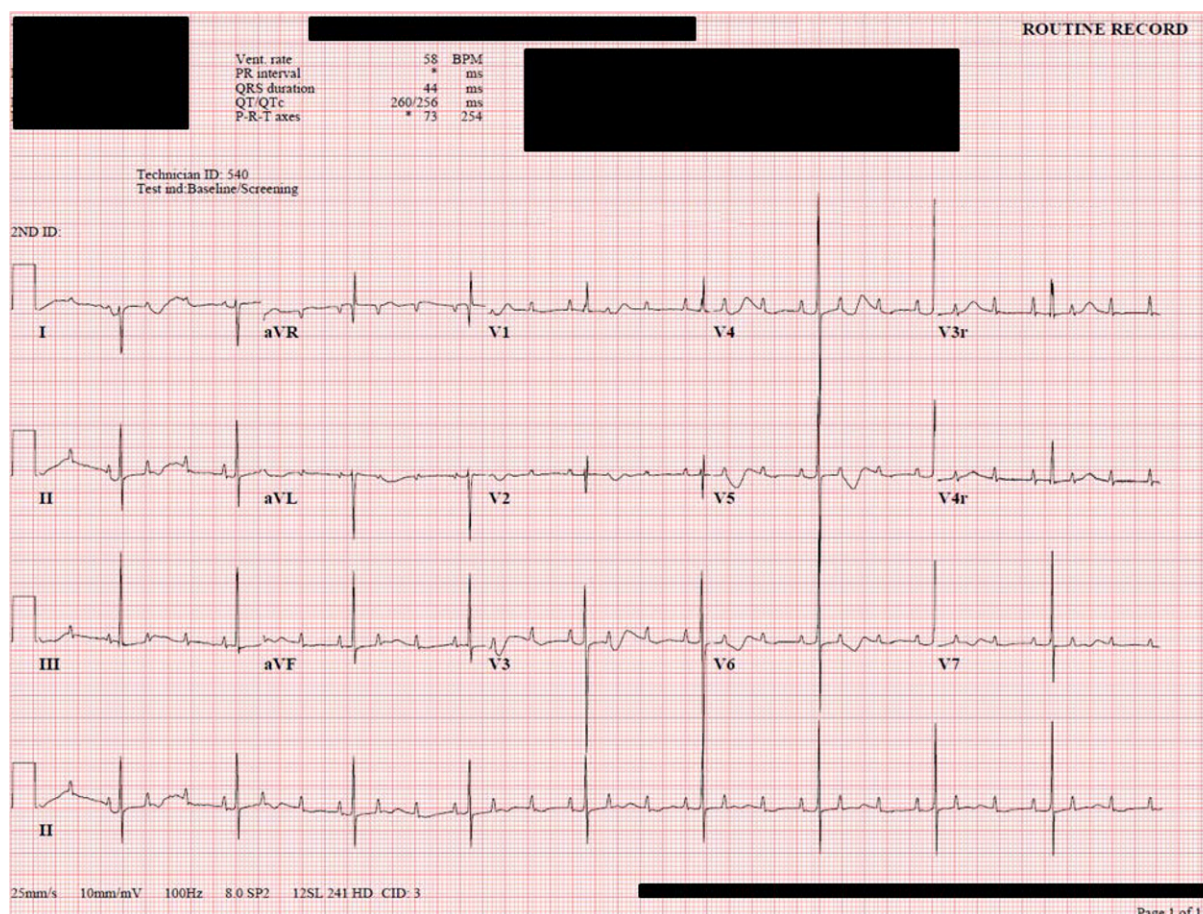


Figure 1. Electrocardiogram of patient obtained on date of birth.

The infant's mother also had been treated with thyroid hormone replacement therapy for hypothyroidism.

In this case, fetal echocardiography performed at 13 weeks of gestation revealed complete heart block (CHB) and large ascites. The mother was started on terbutaline to increase fetal heart rate and dexamethasone to prevent maternal antibody-mediated myocarditis. Serial echocardiography demonstrated CHB at 20, 24, and 28 weeks of gestation with resolution of ascites by 34 weeks of gestation.

The Condition

Neonatal lupus syndrome is an acquired autoimmune disease that occurs in some infants born to mothers with anti-SSA/Ro and anti-SSB/La antibodies associated with a range of autoimmune disorders, including systemic lupus erythematosus, Sjögren syndrome, idiopathic inflammatory myopathies, systemic sclerosis, mixed connective tissue disease, and rheumatoid arthritis. (1)(2) The condition is characterized by congenital heart block, cardiomyopathy, cutaneous lupus lesions, hepatobiliary disease, thrombocytopenia, or other hematologic cytopenias either independently or concurrently. (3)(4)(5)

The most concerning complication is neonatal CHB, which has a prevalence of about 1% to 2% in infants of anti-SSA/Ro-positive mothers, and a recurrence rate of approximately 17% in subsequent pregnancies. (6) Neonatal lupus accounts for 90% to 95% of CHB cases occurring in utero or during the neonatal period. (4)(7)(8)

Cutaneous features of neonatal lupus, which may be apparent at the time of delivery or after the newborn has been discharged from hospital, include multiple erythematous annular lesions or arcuate macules. The rash is often described as a raccoon-eye appearance, with the face being the most common site affected, followed by the palms, soles, or diaper area (Fig 2). (3)(5)(9)

Anti-SSA/Ro and anti-SSB/La autoantibodies are transplacentally transmitted during the second trimester. (10) It is thought that CHB occurs because of opsonization of anti-SSA/Ro and anti-SSB/La autoantibodies to neonatal cardiocytes in utero, thereby inhibiting these cells from participating in the usual clearance of apoptotic cardiocytes. This results in an accumulation of apoptotic cells, promoting inflammation, remodeling, and fibrosis, which may lead to myocarditis or cardiac rhythm impairment. (10)



Figure 2. Photograph of the cutaneous erythematous annular rash of neonatal lupus. (Courtesy of Dr Dawn Davis, Associate Professor of Dermatology and Pediatrics, Mayo Clinic, Rochester, MN.)

Because CHB usually develops between 18 and 24 weeks of gestation, some experts recommend serial fetal echocardiography during this period, with premature atrial contractions and moderate pericardial effusions being concerning for the potential development of CHB. If first- or second-degree heart block is noted on fetal echocardiography, maternal treatment with steroids may prevent progression to CHB. If CHB is detected, treatment with dexamethasone may be initiated to prevent myocarditis, not to treat CHB, because myocarditis is an irreversible complication. (11)(12) The evidence regarding the efficacy of fluorinated steroids in the prevention of mortality in CHB is inconsistent with concerns for adverse effects during pregnancy. (13) In addition, sympathetic β -agonists have been used to increase fetal heart rates in utero, but evidence regarding their impact on mortality is limited. (13)

Lessons for the Clinician

- Cardiac anomalies should be considered in the vigorous neonate with bradycardia despite effective ventilation and normal oxygen saturation.
- While the neonatal resuscitation algorithm recommended by the Neonatal Resuscitation Program is the standard of care for resuscitation of newborns, its reliance on heart rate for guidance of interventions limits its usefulness in the resuscitation of infants with congenital heart block.
- Antenatal care for mothers with anti-SSA/Ro and anti-SSB/La autoantibodies should include serial echocardiography by 18 weeks and beyond.
- Evidence suggests that the use of fluorinated corticosteroids such as dexamethasone may protect against the development of congenital heart block, if the treatment is instituted at an earlier stage.

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American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how specific fetal diagnoses, such as airway abnormalities, abdominal wall defects, myelomeningocele, or severe hydrocephalus might alter prenatal care and intrapartum management (eg fetal intervention "Exit" strategy)
- Differentiate asphyxia from other causes of depression at birth, including drug effects and hypovolemia
- Understand the significance, limitations, and causes of low Apgar scores, including the relationship between Apgar scores and later outcomes in preterm and full-term infants
- Know the proper approach to airway management in the delivery room
- Know the indications for assisted ventilation, including continuous positive airway pressure, immediately after birth and how to assess its effectiveness
- Know the indications for, techniques, and potential complications of chest compression immediately after birth
- Know the indications, contraindications, and methods of administration of drugs used for neonatal resuscitation
- Know the neonatal developmental cardiac manifestations of maternal diseases and maternal drug and environmental exposures
- Know the appropriate techniques to assess cardiovascular function in the fetus and newborn infant
- Differentiate normal from common abnormal electrocardiographic patterns and rhythms in the fetus and newborn infant
- Know the physiologic consequences of an arrhythmia in a fetus or newborn infant
- Know appropriate management of common arrhythmias in the fetus and newborn infant, and understand the potential complications or adverse effects of approaches and drugs used
- Know the mechanism of action of commonly used adrenergic vasopressor and/or inotropic drugs (eg dopamine, dobutamine, epinephrine)

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Case 3: Bradycardia in a Vigorous Newborn

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2 Chronic Testicular Torsion in a Healthy Neonate

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PRESENTATION

A male newborn, weighing 3,180 g, is born via spontaneous vaginal delivery at 38 3/7 weeks' gestation to a 26-year-old, gravida 4, para 3 woman. The pregnancy is uncomplicated and the family history negative. At birth, the right scrotum is swollen and the left testis is not palpable. Scrotal ultrasonography shows a right hydrocele with mild swelling and reduced perfusion of the right testicle (Fig 1A and 1B). The left testicle appears to be in the left inguinal canal with blood flow present (Fig 2A and 2B). He is discharged on day 2 with outpatient follow-up scheduled with urology in 1 week.

The family does not follow up, and the infant presents at 4 weeks of age with bilateral testicular swelling. On examination, the left testis is not palpable and there is diffuse scrotal swelling with no surrounding erythema. Cremasteric reflex is present on the right, but absent on the left. No chordee is noted and transillumination of scrotal skin is negative. Hypertrophy of the right leg is noted, which had been missed on initial examination. The maximum circumference of the right thigh is 16.0 cm compared with 14.0 cm on the left. Hormonal assays including follicle-stimulating hormone, luteinizing hormone, and total testosterone levels are normal. Venous duplex ultrasonography of both lower extremities is negative. Ultrasonography of the abdomen reveals no masses, though there is an incidental grade 1 to 2 dilation of the right renal collecting system. Repeat ultrasonography of the scrotum 29 days later shows perfusion of both testicles with heterogeneity and coarse echotexture (Fig 3A and 3B). Scrotal exploration, right testicular biopsy, and bilateral orchiopexy are performed.

Interestingly no twisting of spermatic cords is noted. Viable seminiferous tubules are noted on initial frozen pathology and histologic examination confirms atrophic and hemorrhagic necrosis of the right testicle consistent with chronic torsion with no evidence of neoplasm.

DISCUSSION

Testicular torsion is twisting of the spermatic cord strictures and subsequent loss of blood supply to the ipsilateral testicles, leading to a surgical emergency. Testicular torsion can be extravaginal or intravaginal. Extravaginal torsion is more common in newborns and involves torsion of the tunica vaginalis and investing outer layers. The weak anchoring between the tunica vaginalis and scrotal wall allows the tunica vaginalis and its contents to rotate around the axis of the spermatic cord. Intravaginal torsion is more common in older children and involves twisting of the testis within the tunica vaginalis.

AUTHOR DISCLOSURE Drs Salman and Goyal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

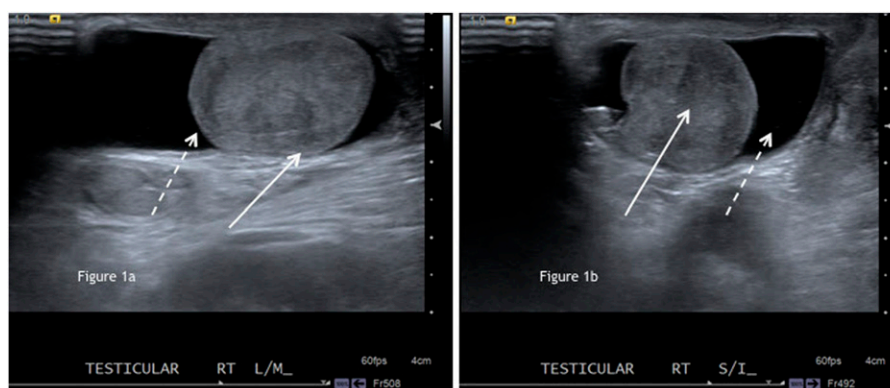


Figure 1. Sagittal views of the right testicle demonstrate course, heterogeneous echotexture and a moderate-sized hydrocele and no focal mass.

Most neonatal torsions are unilateral and only a few cases of bilateral torsion have been described. Seventy percent of unilateral neonatal testicular torsions present within a few hours of birth and 30% present within the first 30 days. Our patient presented after 30 days with appropriate weight gain. He had an abnormal testicular examination and was found to have heterogeneous appearance of bilateral testicles on scrotal ultrasonography, which led to the possibility of a neonatal torsion event. Upon surgical exploration and histologic evaluation, chronic bilateral testicular torsion was diagnosed. Frozen pathology results revealed viable seminiferous tubules with necrosis, which is not consistent with straightforward neonatal testicular torsion. In a typical testicular torsion event, twisting of the spermatic cords causes vascular compromise, leading to ischemia and if not corrected, can result in necrosis and testicular nonviability. Our patient had no twisting of the spermatic cords and normal Doppler flow was noted on ultrasonography, yet a testicular torsion was diagnosed based on histologic results. It is possible there may have been a compromise in testicular vascular flow with restoration of flow in utero, resulting in viable seminiferous

tubules with tissue necrosis. Nevertheless, it is essential to rely on a thorough physical examination to reach the diagnosis and surgical intervention should take place if a diagnosis is in doubt.

The possibility of testicular torsions in healthy neonates is rare, but should be considered. Testicular torsion can cause acute ischemia, hemorrhage, and necrosis, resulting in abnormality of testicular function and infertility. Studies of testicular torsion in older children have shown that about 12 hours of ischemia is sufficient to produce permanent damage to the Leydig cells and compromise of testosterone production. Our case was unique in that our patient did not have a decline in hormonal function despite having torsion 33 days after birth, which was presumably present for days or weeks.

Our patient also had right leg hemihypertrophy. Hemihypertrophy is referred to as hemihyperplasia involving abnormal growth of cells in one or more body parts. Infants with isolated hypertrophy have been noted to have an increased risk for developing embryonal tumors especially Wilms tumor and hepatoblastoma. Abdominal and venous ultrasonography did not reveal any tumors. Genetic

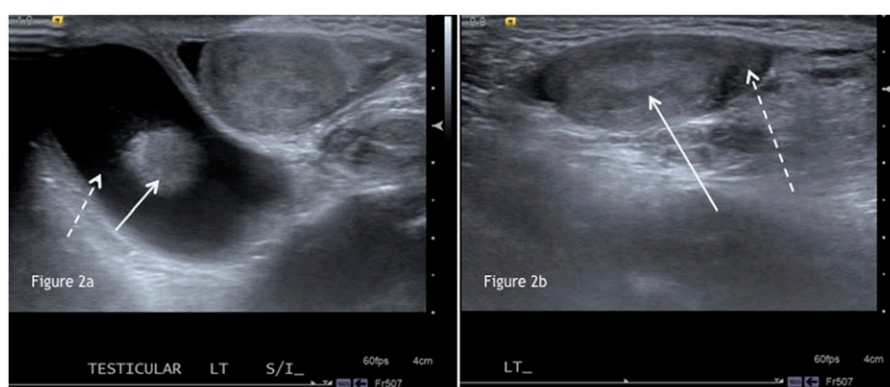


Figure 2. These transverse and sagittal images of the left testicle demonstrate coarse heterogeneous echotexture with a trace hydrocele and no focal mass.

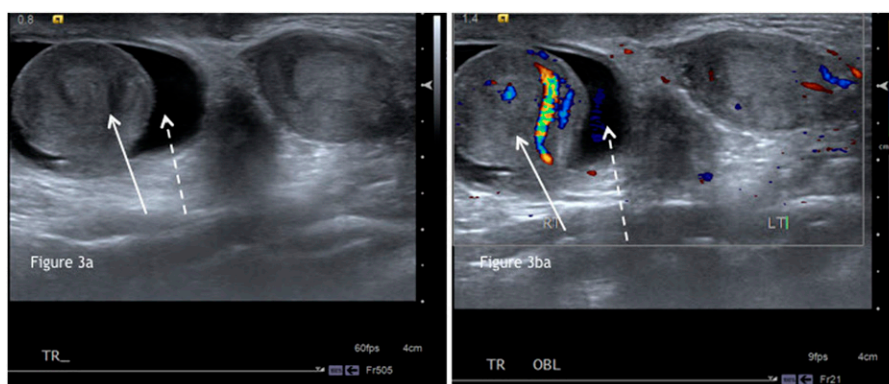


Figure 3. These images demonstrate the bilateral testes in the transverse plane. Again, there is a heterogeneous, coarse echotexture of testis bilaterally. The Doppler image shows flow present within both testicles.

evaluation is planned, however, the family has not followed up for evaluation.

Conclusion

Neonatal testicular torsion is a surgical emergency occurring within the first few hours after birth and is associated with a poor prognosis. Rare cases of bilateral testicular torsion with normal growth and development have been described. We report a unique case of chronic testicular torsion in a healthy neonate with an incidental finding of right leg hypertrophy. Clinical diagnosis of testicular torsion in neonates can be a challenging task because most cases are asymptomatic; therefore, it is important to perform a detailed testicular physical examination and use ultrasonography as an adjunct for diagnosis. Although rare, testicular torsion should be considered in the differential diagnosis of a thriving neonate who presents with swollen testes.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the neonatal complications of abnormal presentations (breech, shoulder dystocia, etc).

Suggested Readings

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Case 2: Chronic Testicular Torsion in a Healthy Neonate

Ashima Goyal and Bassel Salman

NeoReviews 2019;20:e667

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Coexisting Cystic Lesions of Lung in a Term Neonate: A Management Dilemma

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AUTHOR DISCLOSURE Drs Raut, Aakriti Soni, Badatya, Saluja, Modi, and Arun Soni have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term, 38-week-gestation, small-for-gestational age female infant weighing 2,135 g is delivered vaginally by a primigravida woman with an antenatal history of deranged Doppler flows. Resuscitation is not required at birth because the infant has normal Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. Prenatal ultrasonography reports the presence of congenital pulmonary airway malformation (CPAM) on the left side, which regressed after steroid treatment in the third trimester. Delivery room postnatal examination suggests that the heart sounds are prominent on the right side of the precordium with the infant maintaining target oxygen saturation on room air with no signs of respiratory distress. She is admitted to the NICU for observation and further evaluation of mediastinal shift.

CASE PROGRESSION

In the NICU, chest radiography reveals hyperinflated left lung with shifting of mediastinum to the right (Fig 1). Computed tomographic (CT) imaging reveals left lower lobe CPAM with a posterior mediastinal cyst compressing the left main bronchus (Fig 2). Echocardiography and ultrasonography of the abdomen and cranium are performed to rule out other associated congenital anomalies, and are found to be normal. At 20 hours after delivery, she develops mild respiratory distress but does not require any respiratory support. Forty-eight hours after admission, the infant undergoes bronchoscopy to locate the



Figure 1. Chest radiograph showing hyperinflation of left lung with mediastinal shift to the right.

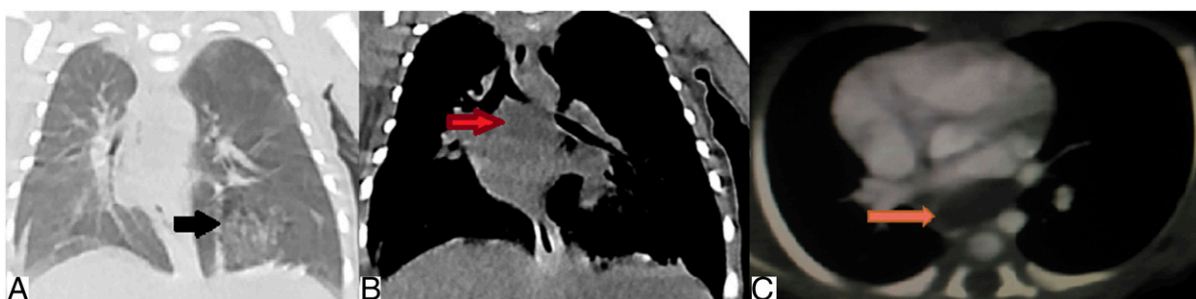


Figure 2. A–C. Computed tomography scan showing the presence of congenital pulmonary airway malformation (black arrow) and posterior mediastinal cyst (red arrow) with mediastinal shift.

site of airway obstruction, which reveals the presence of a bluish mass compressing the left main bronchus (Fig 3). This leads us to suspect a hemangioma or vascular malformation compressing the bronchus. However, CT pulmonary angiography rules out the presence of any such vascular malformation. The possibilities are thus narrowed down to the presence of a bronchogenic cyst as the infant continues to have mild respiratory distress with hyperinflated left lung and mediastinal shift to the right. Expert opinions of pediatric and cardiothoracic vascular surgeons are therefore sought and accordingly the infant undergoes surgical exploration. The consensus of the team is to perform a resection of the cystic lesion compressing the left bronchus, because it is believed that simultaneous resection of both cysts (CPAM and bronchogenic cyst) may put the infant under too much stress. Possibly the symptoms most likely to be seen are due to the compression effect of the bronchogenic rather than regressing CPAM. On the fourth day after delivery, after counseling the parents and obtaining their consent, the surgical team proceeds with a left thoracotomy, and intraoperative findings show an intramural cyst near carina, compressing the left bronchus. Because the cyst and bronchus share a common muscular wall, the cyst is excised, saving the muscle over the bronchus. Biopsy of the excised cyst shows features similar to those of the foregut and it is lined by pseudostratified ciliated columnar epithelium, which confirms the diagnosis of bronchogenic cyst. The infant continues to receive mechanical ventilation after surgery. However, on the second postoperative day, she undergoes extubation but does not tolerate it and develops stridor with severe respiratory distress, thereby needing re-intubation. A repeat flexible bronchoscopy is undertaken, which reveals subglottic edema, for which she is treated with systemic steroids and epinephrine nebulization. After this, she undergoes successful extubation on the second day of steroid therapy. The infant is now being discharged on day 15 after birth. The potential complications of CPAM, such as repeated chest infections, pneumothorax, and malignant potential,

including their danger signs, have been explained to the infant's caregivers. A follow-up plan is made with regular assessment of growth monitoring and plan for an elective resection of the lower lobe at 6 months of age or earlier if required.

DISCUSSION

Incidence of congenital cystic lesions of lung is 1 in 25,000 to 35,000 live births. (1) CPAM is often described as a hamartomatous lesion because of abnormal development of the tracheobronchial tree. It develops during the pseudoglandular phase (7–17 weeks) of fetal lung development. Depending on the site of origin and histopathology, it is classified (Table 1) into 5 types. (2) Another classification proposed (Table 2) is based on antenatal ultrasonography. (3) This is useful in guiding the clinician to manage the antenatally diagnosed cases. (4) The 2 most important features for its diagnosis are 1) its connection to the tracheobronchial tree, and 2) vascular blood supply from the pulmonary circulation.

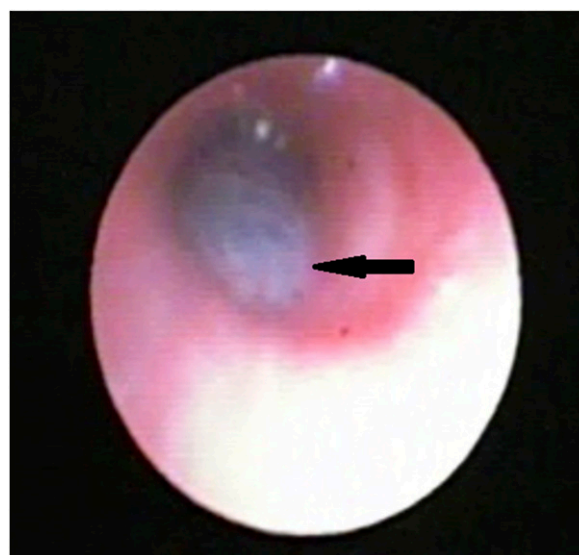


Figure 3. Bronchoscopy image showing extraluminal bluish mass (black arrow) on left main bronchus.

TABLE 1. Classification of Congenital Pulmonary Airway Malformation Based on Site of Origin From Tracheobronchial Tree as Described by Stocker et al (2)

TYPE	SITE OF ORIGIN
Type 0	Trachea
Type 1	Distal bronchi/proximal bronchiole
Type 2	Bronchioles, up to terminal bronchiole
Type 3	Alveolar duct/proximal acini
Type 4	Distal acini

Bronchogenic cyst arises as an abnormal bud from the primitive foregut. Depending on its timing of separation from the foregut, it may form an extrapulmonary cyst by migrating into the mediastinum if separated early, or alternatively, it forms an intrapulmonary bronchogenic cyst when separated late. Antenatally it can be diagnosed with ultrasonography wherein it appears as an anechoic, unilocular, intrathoracic cyst. Such antenatal diagnosis of cysts helps in their management and prognosis, because depending on their size, they may compress the lung or heart parenchyma, leading to pulmonary hypoplasia or hydrops, respectively. (1) Most patients remain asymptomatic after birth in case of small cysts. Coexistence of CPAM and

TABLE 2. Classification of Congenital Pulmonary Airway Malformation Based on Antenatal Ultrasonography Proposed by Adzick et al (3)

TYPE	SIZE	APPEARANCE	PROGNOSIS
Macroscopic	>5 mm	Anechoic surrounded by hyperechoic lung	Grows slowly Has a favorable prognosis
Microcystic	<5 mm	Homogenous solid mass, hyperechoic as compared to lung parenchyma	Larger in size and grow rapidly, often associated with mediastinal shift, pulmonary hypoplasia, polyhydramnios and hydrops Has a poor prognosis

TABLE 3. Differentiation Between Congenital Pulmonary Airway Malformation (CPAM) and Bronchogenic Cysts

CPAM	BRONCHOGENIC CYST
Usually air filled unless infected	Usually mucous filled unless infected
Cyst wall is thinner	Cyst wall is thicker
Surrounded by island of cartilage only	Surrounded by cartilage, smooth muscle, elastic tissue, mucous glands

bronchogenic cyst is very rare and unusual, (5) and patients may be symptomatic with either. In our case, despite the coexistence of CPAM and bronchogenic cyst, antenatal ultrasonography and fetal magnetic resonance imaging missed the bronchogenic cyst. Although CPAM was reported to be regressing, postnatal CT scan diagnosed the presence of both these cysts. Looking at the small size of CPAM, it appears that the hyperinflated left lung and compressed left main bronchus was caused by the bronchogenic cyst, resulting in mediastinal shift and respiratory distress in the infant described herein. Sometimes it may be difficult to differentiate CPAM types 0 and 1 from bronchogenic cyst. The differentiating points (Table 3), however, help in identifying the exact nature of the cyst.

Prognosis of cystic lung lesions depends on histopathology of the lesion, other associated congenital anomalies, presence or absence of hydrops, signs of cardiovascular compromise, and pulmonary hypoplasia due to mass effect. Survival to delivery is reported in 95% of cases of CPAM. In fetuses that do not develop hydrops, postnatal survival has been reported to be nearly 100%. In fetuses with hydrops that undergo prenatal intervention, survival has been reported at a mean of 80%, with rates up to 100% among those treated with thoracocentesis. Neonatal survival was 69%. (6) Postnatal management depends on whether the infant is symptomatic. If symptomatic, surgical intervention is definitive after stabilization. However, in asymptomatic cases, elective resection is safe and prevents the risk of symptom development, which may result in a more complicated surgery and recovery. (7)

Lessons for the Clinician

- Although rare, different types of cystic lung disease can be present together.
- It is very difficult for the clinician to make out which lesion is primarily responsible for the symptoms. Proper clinical assessment and investigations may help the

clinicians and surgeons to make a rational decision because multiple surgeries at the same time may not be tolerated by the infant.

- Although the infant may remain asymptomatic, surgical excision of congenital pulmonary airway malformation is necessary between 6 months and 1 year of age because of the future risk of recurrent chest infection, pneumothorax, and malignancy.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the appropriate management for an infant with congenital malformations of the lung, including congenital pulmonary lymphangiectasia, and the cystic lung diseases, such as congenital lobar emphysema, cystic adenomatoid malformation, and mediastinal tumors.

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2 Dilated Stomach in an Infant with Failure to Thrive

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Ramesh Santhanakrishnan, MBBS, MS, DNB (Gen Surg), MCh (Paed Surg)[†]

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PRESENTATION

A 2-month-old male infant undergoes anoplasty for low anorectal malformation. At follow-up, his weight gain is found to be inadequate. However, he is feeding well, his urine output is noted to be adequate, and he has no diarrhea or constipation. Neoanus is healthy and functioning normally. He has no history of vomiting or abdominal distention. Lactation counseling is given and the infant's family is advised to bring him in for regular follow-up for growth monitoring. However, his parents bring him in for a follow-up at 4 months of age because he had been admitted to an outside hospital for pneumonia at age 3 months. His investigations during pneumonia admission are reviewed. Chest radiography shows right upper lobe consolidation with a hugely dilated stomach (Fig 1). There is no history of cough, choking, or blue discoloration of the skin while feeding. There is no history of abdominal distention or vomiting.

On examination, his heart rate is 120 beats/min and respiratory rate is 28 breaths/min. The respiratory system, cardiovascular system, and abdominal examination findings are normal.

Routine blood investigations are normal. Upper gastrointestinal contrast study shows dilated stomach, normal-caliber duodenum with easily emptying stomach, and no evidence of gastroesophageal reflux. Pull-up esophagogram reveals no fistulous communication with the esophagus.

DISCUSSION

Differential Diagnosis

The causes for the dilated stomach in an infant with anorectal malformation with failure to thrive can be gastric outlet obstruction secondary to pyloric stenosis, duodenal stenosis, or gastric volvulus; or an H-type tracheoesophageal fistula may be responsible. The presence of respiratory tract infection in the infant led to a high degree of suspicion of H-fistula even though there was no associated cough or choking episodes while feeding. Upper gastrointestinal contrast study ruled out gastric outlet obstruction, which further strengthened our suspicion of H-fistula even with the normal pull-up esophagogram. Bronchoscopy is the investigation of choice for H-fistula, which helped us diagnose the condition even without the classic presentation.

AUTHOR DISCLOSURES Drs Radhakrishna, Parashar, Goel, and Santhanakrishnan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

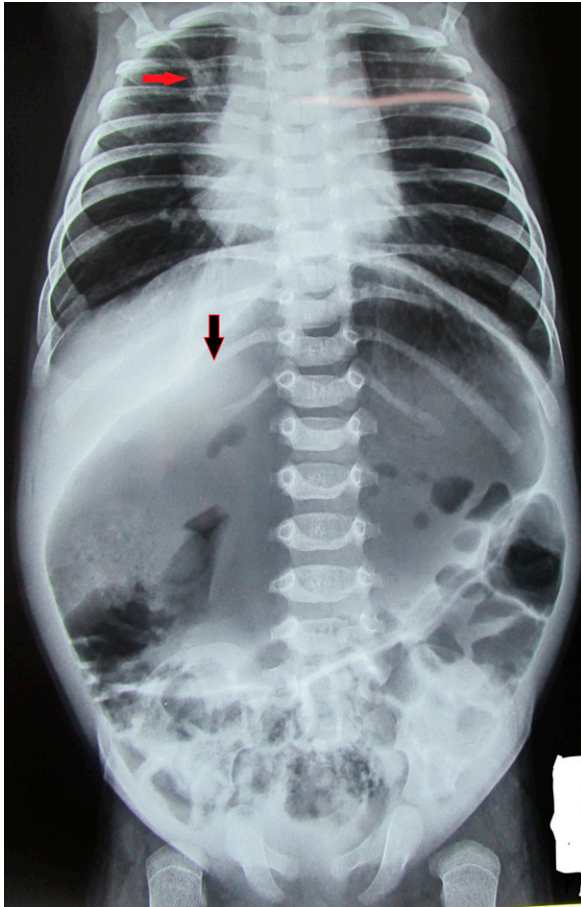


Figure 1. Radiograph of the chest and abdomen showing right upper lobe consolidation (red arrow) with a hugely dilated stomach (black arrow).

Actual Diagnosis

Because of the high suspicion for H-type tracheoesophageal fistula, a diagnostic bronchoscopy is performed, which revealed an H-type tracheoesophageal fistula (Fig 2).

The Condition

The H-type fistula is an uncommon type of tracheoesophageal fistula accounting for 4% of cases. The child usually presents with coughing, choking, and cyanosis during feedings. However, the condition is seldom diagnosed in the neonatal period because the symptoms coincide with gastroesophageal reflux and faulty feeding, which are more common. These infants develop recurrent episodes of pneumonia which are also common in gastroesophageal reflux. A dilated stomach on radiography or contrast study tends to give a clue toward H-fistula. Pull-up esophagogram is beneficial, but it is practically difficult to perform in an actively crying child. The close apposition of the trachea to the esophagus and the obliquity of the fistula keeps the fistula occluded for most of the time. The fistula opens when

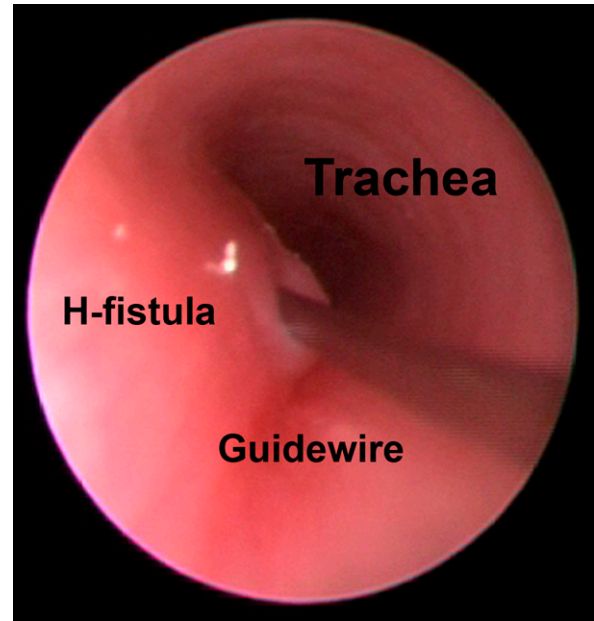


Figure 2. Bronchoscopy showing trachea, with the fistula being cannulated by a guidewire.

the esophagus moves up during swallowing, allowing esophageal content to enter the trachea. Hence, the esophagogram is not a very sensitive investigation and often misses the fistula (50% cases). Bronchoscopy is the diagnostic procedure of choice, which gives a magnified vision and allows cannulation of the fistula. This helps in easy identification of the fistula during surgical exploration.

Management

Surgical repair is the treatment of choice. The fistula can be approached through the right-sided low cervical incision. Rarely, a right thoracotomy is required in cases of thoracic level fistula. Operative complications include tracheal edema, damage to the recurrent laryngeal nerve, esophageal leak, and recurrence.

Patient Course

The infant underwent an open repair of the tracheoesophageal fistula. The postoperative period was uneventful. He was thriving and had no issues at the 6-month postoperative follow-up.

Lessons for the Clinician

- H-type tracheoesophageal fistula is a life-threatening disease that can present without the classic cough or choking while feeding.
- A high index of suspicion is needed to diagnose and treat H-fistula to prevent dangerous complications.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathophysiology of air leaks
- Recognize the clinical, laboratory, and imaging features of air leaks
- Recognize the clinical features of extrapulmonary causes of respiratory distress
- Recognize the imaging features of extrapulmonary causes of respiratory distress

- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress

Suggested Reading

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Case 2: Dilated Stomach in an Infant with Failure to Thrive
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Santhanakrishnan
NeoReviews 2019;20:e412
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Dome-Shaped Papules and Nodules in Monozygotic Twins

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Pedro Pasquel-García, MD,† Maria T. García-Romero, MD, MPH*

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PRESENTATION

A pair of male monozygotic twins is born at 38 weeks of gestation via a cesarean delivery to a 29-year-old woman with normal prenatal care. Three ultrasound scans are obtained during pregnancy, confirming monochorionic-monoamniotic twin gestation from the first study, and the presence of an amniotic band that does not affect any product in the second ultrasound scan. The rest of the perinatal history is unremarkable.

Since the first week after birth their mother has noticed small lesions on the face and trunk. They are seen in the hospital at 15 days of age. On physical examination, they have yellowish-brown, soft dome-shaped papules and nodules, 0.5 to 2 cm in diameter, affecting the head, trunk, and extremities. Twin number 1 has 21 lesions and twin number 2 has 25 (Figs 1 and 2). They are asymptomatic, neither twin has hepatosplenomegaly or enlarged lymph nodes, and neither their parents nor grandparents have similar skin lesions.

A biopsy of one of the lesions shows a massive dermal infiltrate of round, medium-sized mononuclear cells with abundant cytoplasm and reniform nuclei that extended to the subcutaneous tissue (Fig 3A). Immunohistochemistry was positive for CD68 (Fig 3B), CD33, and CD163; and negative for CD1a, compatible with non-Langerhans cell histiocytosis (LCH) phenotype. Results of abdominal ultrasonography, complete blood cell count, and ophthalmologic assessment were all reported normal in both children. Viral load for cytomegalovirus and Epstein-Barr virus were negative.

Laboratory tests in both twins, combined with the biopsy and examination findings, confirm the diagnosis.

DISCUSSION

Juvenile xanthogranuloma (JXG) is the most common non-LCH. (1)(2) The non-Langerhans cell histiocytosis (non-LCH) phenotype includes a group of disorders defined by the accumulation of histiocytes that do not meet the phenotypic criteria for the diagnosis of Langerhans cells. (1)(3)

JXG mainly affects children younger than 2 years and is characterized by single (67%) or multiple reddish-yellow papules predominantly located on the head and neck (42%) followed by the trunk (26%) and lower (16%) and upper extremities (15%), (4) and, rarely, in other organs. This lesion tends to spontaneously regress. (5)(6) The term “xanthogranuloma” refers to the histologic findings of lipid-laden histiocytes with a vacuolated, foamy xanthomatous cytoplasm and giant cells. (6)

AUTHOR DISCLOSURE Drs Campos-Cabrera, Morán-Villaseñor, and Pasquel-García have disclosed no financial relationships relevant to this article. Dr García-Romero has disclosed that she receives speaker honoraria from Pierre Fabre Mexico and IFC Cantabria. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Multiple yellow-red nodular lesions in the head, limbs, and trunk of both twins.

JXG affects all races, with a slight male predominance (1.5:1). (6) The incidence is not established. Its pathogenesis is unknown, but there are theories regarding a reactive histiocytic response to a physical or infectious stimulus, (2) such as varicella and cytomegalovirus, (7)(8) or a genetic predisposition. (3)(5)(9)

In 5% to 17% of cases, lesions may appear soon after birth and in 40% to 70% of patients, during the first year of age. (2)(6) The lesions of JXG present as well-demarcated reddish papules or nodules varying from 0.5 to 2.0 cm in diameter, with giant lesions (up to 10 cm); these papules eventually become yellowish plaques or macules as they involute spontaneously. (3)(5) Multiple cutaneous lesions, like those seen in the current patients, are seen in approximately 5% to 7% of patients. (4)(10)

Systemic involvement occurs in 5% of patients, (8) most frequently the eyes (0.3%–0.5% of patients with JXG), (6) but the liver, oropharynx, lungs, spleen, muscle, heart, kidneys, retroperitoneum, and central nervous system can also be affected, with clinical manifestations including obstructive jaundice, liver dysfunction, coagulopathy, hypersplenism, and bicytopenia. (5)



Figure 2. Dome-shaped yellowish plump nodules.

The risk for ocular involvement is highest in children younger than 2 years with multiple skin lesions (>3 lesions) and the micronodular form of JXG (lesions ≤10 mm in contrast to the macronodular >10 mm). (4) Most ocular JXGs occur on the iris, followed by the eyelid and orbit. (4) (6) Orbital involvement is rare and occurs in the perinatal period with unilateral exophthalmos. (6) Other clinical data include a spontaneous hyphema because JXG is the most frequent cause of spontaneous hyphema in children. Unlike cutaneous lesions, intraocular JXGs do not resolve spontaneously and may result in severe secondary glaucoma and vision loss. (4)

Disseminated JXGs have been associated with neurofibromatosis type I, epilepsy, Niemann-Pick disease, urticaria pigmentosa, and juvenile myelomonocytic leukemia. (5)(11) Children with neurofibromatosis type I and JXG have been estimated to have a 20- to 32-fold higher risk for juvenile chronic myelogenous leukemia. (4)(6)

The diagnosis of disseminated JXG is clinical; however, it may be difficult to clinically distinguish it from nodular LCH; therefore, a skin biopsy is recommended. (6)(12) Other differential diagnostic considerations include mastocytoma, benign cephalic histiocytosis, and xanthoma disseminatum. (6)

Histologic examination revealed an accumulation of histiocytes intermingled with Touton-type giant cells and foam cells, and a variable number of eosinophils and lymphocytes; in early lesions, Touton cells can be absent, similar to our patients. (2) These cells are characteristic of xanthomatous lesions, are seen as large multinucleated cells with a ring of nuclei surrounded by foamy (lipids) cytoplasm, and are formed by the fusion of macrophages. (2)(6)

Immunohistochemical staining is negative for S100 and CD1a (both markers of Langerhans cells) and positive for CD68, CD163, CD14, vimentin, and (variably) factor XIIIa. (1)(5)(10)

The prognosis in patients without systemic involvement is favorable, with most cutaneous lesions spontaneously regressing without any therapeutic intervention within 6 months to 3 years. (2)

PATIENT COURSE

With conservative management, the twins' lesions regressed spontaneously over the following months. After 20 months of follow-up, they have not developed new skin lesions or systemic involvement.

Lessons for the Clinician

- Monozygotic twins have an unusual presentation that supports the hypothesis of a genetic predisposition for a

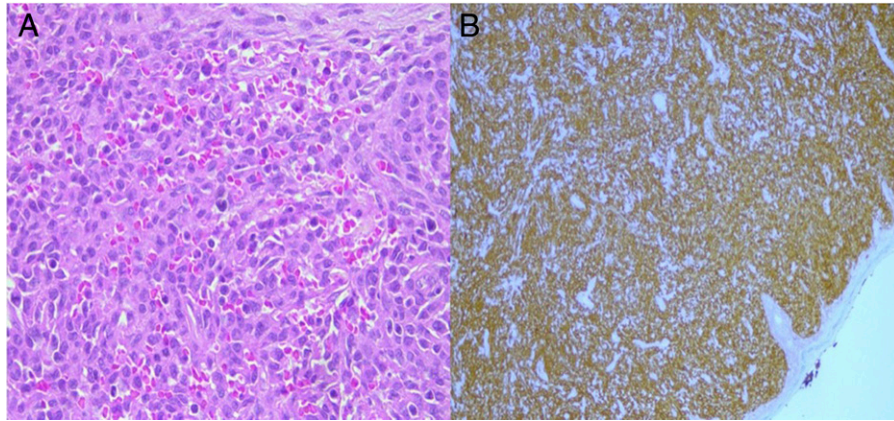


Figure 3. A. Massive histiocytic infiltrate that extends to the subcutaneous tissue (H&E stain, magnification $\times 40$). B. Positive immunohistochemistry for CD68 (magnification $\times 10$).

reactive histiocytic granulomatous response to an unknown stimulus; however, further studies are warranted.

- Disseminated juvenile xanthogranuloma has a benign course and tends to be self-limiting; however, it is necessary to follow up patients to rule out systemic involvement and potential associations with other diseases.
- Skin biopsy is required to help exclude other disorders.
- A complete evaluation is required to determine the presence or absence of extracutaneous involvement.
- Children younger than 2 years and with multiple lesions have a higher risk of ocular involvement, therefore, they must be evaluated by a pediatric ophthalmologist.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the cutaneous and laboratory manifestations, including imaging studies, and management of non-Langerhans cell histiocytoses.

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Case 1: Dome-Shaped Papules and Nodules in Monozygotic Twins

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3 Early Severe Jaundice in a Term Infant

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AUTHOR DISCLOSURE Drs Cohoon, Delle Donne, Whiteway, and Carr have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An appropriate-for-gestational age (AGA) African American female infant is born at term via elective, repeat cesarean section at 39 weeks' gestation to a gravida 2, para 2 woman. The mother's pregnancy had been complicated only by gestational hypertension, and maternal antenatal testing results were unremarkable. Maternal blood type is O positive with a negative antibody screen during pregnancy. Meconium fluid is noted at delivery; however, the infant is vigorous with a strong cry and requires only routine resuscitation with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. After resuscitation, the infant makes a transition to routine couplet care with an anticipated 48-hour stay.

A cord blood sample is sent for blood type and direct antiglobulin test (DAT) per hospital protocol secondary to maternal blood type finding of B-negative type with a negative DAT result. Her first 24 hours are uneventful with direct breastfeeding every 2 to 3 hours, 2 documented voids, 3 stools, and minimal weight loss. All documented vital signs and examination results are normal for a term newborn. At 24 hours after birth, a transcutaneous bilirubin test is attempted per standard newborn care plan, with the resulting value too high to detect. Serum total and direct bilirubin concentrations are found to be 21.7 mg/dL (360 μ mol/L) and 0.6 mg/dL (10 μ mol/L), respectively. The infant is transported directly to the NICU for continued management and preparation for possible exchange transfusion.

DIFFERENTIAL DIAGNOSIS

With any case of hyperbilirubinemia, especially with early-onset or rapidly increasing levels, it is important to keep a broad differential to avoid missing benign versus more severe causes of jaundice. Categorizing by time of onset into 3 categories can be useful in establishing a differential diagnosis. These categories are based on newborn age: less than 24 hours after birth, between 24 and 72 hours after birth, and beyond 72 hours after birth. (1)(2)

Neonatal jaundice or hyperbilirubinemia in the first 24 hours is pathologic and should prompt immediate evaluation by the medical team. A thorough physical examination of the patient and review of maternal medical records, including blood type, will help direct appropriate laboratory tests and medical management. Sepsis and hemolytic disease of the newborn, as well as glucose-6-phosphate dehydrogenase (G6PD) deficiency are a few of the causes of early-onset neonatal jaundice (Table).

TABLE. Time to Onset of Pathologic Indirect Hyperbilirubinemia

TIME AFTER BIRTH, H	CAUSES OF HYPERBILIRUBINEMIA
<24	Sepsis, hemolytic disease of the newborn, glucose-6-phosphate dehydrogenase deficiency
24–72	Sepsis, physiologic, polycythemia, cephalohematoma, increased enterohepatic circulation
>72	Sepsis, breast milk jaundice, metabolic disorders, extrahepatic biliary atresia

CLINICAL COURSE

Laboratory evaluation, including complete blood cell count (CBC), reticulocyte count, serum glucose, blood culture, blood gas, and repeat serum total bilirubin were sent upon admission, and the infant was given empiric antibiotics. Triple phototherapy, including a phototherapy blanket and 2 banks of lights, was initiated. A single 10-mL/kg bolus of normal saline (0.9%) was given and the infant was placed on maintenance intravenous fluids at a total fluid goal of 80 mL/kg per day. Serial neurologic examination findings remained unremarkable, and the patient showed no signs of lethargy, hypertonia, arching, retrocollis, or temperature instability. Immediate recheck of the total serum bilirubin after fluid administration showed a decrease to 21 mg/dL and a hematocrit value noted in free-flowing venous blood gas sample was 35%. Initial attempts to obtain a CBC and reticulocyte count were rejected because the increased bilirubin interfered with the laboratory's ability to interpret the results. While preparing to receive a double-volume exchange transfusion, high-intensity phototherapy was continued and a repeat serum total bilirubin 2 hours later showed a decrease to 18.8 mg/dL (321 μ mol/L). An umbilical line was placed in consideration for potential exchange transfusion, which was ultimately deferred.

The first CBC result showed a hemoglobin of 11.7 g/dL (117 g/L), hematocrit of 35%, platelet count of $95 \times 10^3/\mu$ L ($95 \times 10^9/L$), and a reticulocyte count of 40.8% (Fig 1). Total serum albumin was 3.4 g/dL (34 g/L) with an albumin-bilirubin ratio of 7.5 mg/g. Despite the initial negative result seen in the cord blood sample, the type and screen were repeated in the infant because of the clinical suspicion of antibody-mediated destruction from ABO incompatibility. The infant sample resulted in a blood type of B negative with a strong anti-B antibody. Because of the immune-mediated process, evidence of brisk hemolysis with high reticulocyte count, and significant hyperbilirubinemia, the decision was made to treat with 0.5 g/kg of intravenous immunoglobulin. Over the next several days, the infant's serum bilirubin reached a plateau near 14 to 15 mg/dL (240–257 μ mol/L). After 7 days of phototherapy, the patient was discharged with

a bilirubin of 11.8 mg/dL (202 μ mol/L; Fig 2) and hemoglobin of 9 g/dL (90 g/L). An expedited newborn screen returned with a presumptive positive result for G6PD A-negative genotype. Subsequent testing weeks later revealed Gilbert disease, which is not normally associated with significant neonatal hyperbilirubinemia, but when combined with G6PD, causes a significant rise in unconjugated bilirubin levels in the neonate.

THE CONDITION

Bilirubin is produced by the breakdown of red blood cells (RBC) and the catabolism of heme by the reticuloendothelial system. In its unconjugated state, bilirubin is released into the circulation where it binds to albumin and is transported to the liver. Once it reaches the liver, this bilirubin-albumin complex is transported into the hepatocyte where it combines enzymatically with glucuronic acid in a reaction catalyzed by uridine diphosphate-glucuronosyl transferase (UGT1A1). Because of the decreased functioning of this enzyme in neonates, increased RBC turnover, and increased enterohepatic circulation, jaundice is seen to some extent in nearly all newborns. In most cases, transient jaundice is a benign condition and does not require treatment. However, in some cases, bilirubin rises to levels sufficient enough to cross the blood-brain barrier and deposit in the basal ganglia, causing acute and chronic bilirubin encephalopathy. This pathologic staining of the brain is called *kernicterus*, and although rare, remains a completely preventable cause of cerebral palsy, because high levels of bilirubin can affect the developing nervous system. While most hyperbilirubinemia is transient and treated easily with phototherapy, certain conditions may predispose a neonate to rapid increase in bilirubin that may require other therapies, including, but not limited to, pharmacologic treatment with agents such as phenobarbital or ursodeoxycholic acid or exchange transfusion. (3)

ABO Incompatibility

In the case of ABO incompatibility, a DAT should be performed to identify potential hemolytic disease of the

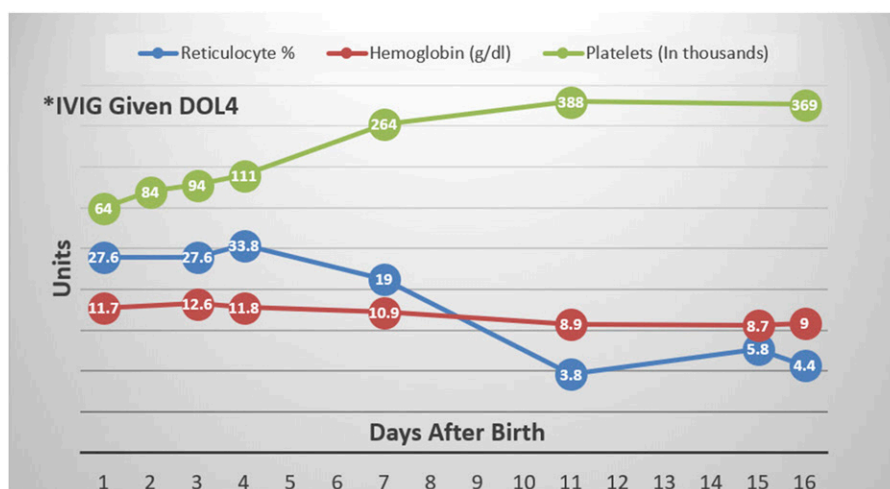


Figure 1. Trends seen in hemoglobin, platelets, and reticulocyte counts in the patient over the first 16 days after birth.

newborn (HDFN). However, an initial negative test result in the setting of increased clinical suspicion may prompt repeat laboratory testing as in the case described here. HDFN is caused by destruction of RBCs in the neonate because of maternal immunoglobulin G antibodies. Allo-immune HDFN can involve minor and major blood group incompatibilities, but usually involves the major blood groups including groups of Rhesus D (Rh), A, and B. In affected neonates, the clinical course can range from self-limited mild disease to life-threatening anemia. In most neonates, the first sign of disease is jaundice within the first 24 hours after birth. Patients with ABO incompatibility generally have a milder course and less severe disease compared with the Rh D incompatibility because

of the presence of A and B antigens on other hemato-poietic cells. (4)(5) African Americans with ABO incompatibility and DAT positivity may be at risk for severe hyperbilirubinemia associated with hemolytic disease. (6)(7)

Thrombocytopenia and ABO Incompatibility

Severe cases of HDFN are associated with thrombocytopenia likely related to consumption with hypersplenism and increased RBC production limiting marrow space. A and B blood group antigens are weakly expressed on platelets, but approximately 1% of the population will strongly express antigens on their platelets. In cases of ABO incompatibility there may be a component of

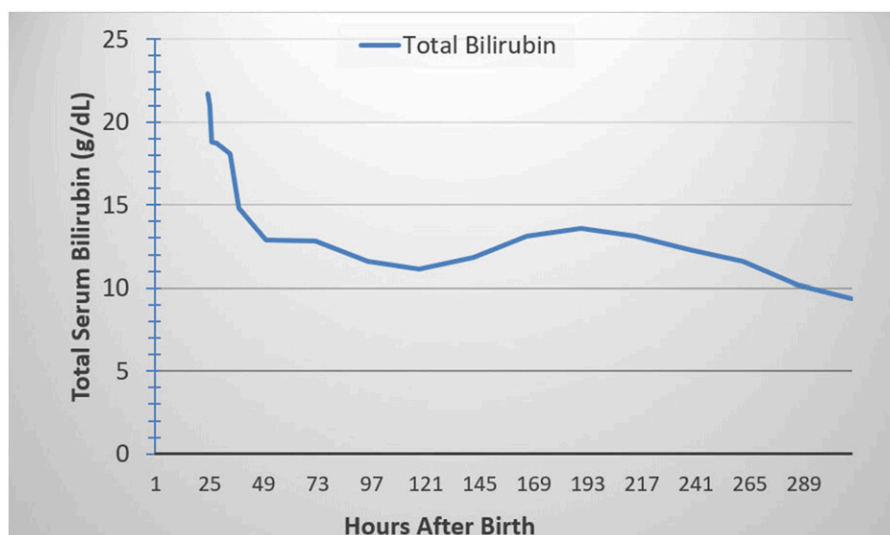


Figure 2. Trends seen in total bilirubin concentrations in the first 2 weeks after birth.

alloimmune destruction from the blood group-specific antibody. In such cases, treatment with intravenous immunoglobulin is therapeutic in both destroying RBCs and preventing severe thrombocytopenia. (8)

Glucose-6-Phosphate Dehydrogenase Deficiency

G6PD is the most common enzymatic disorder of RBC. It is a genetic disorder inherited in an X-linked fashion with wide variance in clinical expression. G6PD catalyzes the initial step in the hexose monophosphate shunt (HMP) by oxidizing the glucose-6-phosphate to 6-phosphogluconolactone to reduce nicotinamide adenine dinucleotide phosphate (NADP) to NADPH. The HMP shunt is the only source of NADPH in RBCs and prevents accumulation of superoxide radicals that can lead to hemolysis. Newborns with G6PD deficiency have a higher incidence of jaundice. Although the peak levels of hyperbilirubinemia occur at 2 to 3 days, the initial signs may be present early on. Kaplan et al showed that in G6PD alone there is a 9.7% rate of hyperbilirubinemia. G6PD is inherited in an X-linked recessive pattern. This results in pathology in affected males and perpetuation of carrier states in females. However, if a carrier/affected woman and an affected man conceive a daughter, she has a 100% chance of inheritance if the mother is affected and a 50% chance if the mother is only a carrier. (9)(10)

G6PD and Gilbert

Patients with Gilbert syndrome have decreased bilirubin conjugation because of a mutation in the bilirubin-UGT (*UGT1A1*) gene. *UGT1A1* conjugates bilirubin to glucuronic acid, converting the bilirubin into a water-soluble form that is readily excreted in bile. This defect causes a decrease in excretion and a subsequent increase in serum bilirubin levels. This is usually not clinically significant in the newborn, but in patients with G6PD and Gilbert *UDPGT1* genotype, the incidence of hyperbilirubinemia increases to 31.6% in the heterozygous mutation and 50% in the homozygous mutation. (11) In our case, a screening for Gilbert was performed because of the disproportionately high level of bilirubinemia and clinical suspicion.

Lessons for the Clinician

- Neonatal hyperbilirubinemia, while common, requires consideration of a broad differential diagnosis, especially if it has a severe early onset (first 24 hours after birth).
- Severe jaundice that occurs in the first 24 hours after birth should be treated as pathologic. The differential

diagnosis should include sepsis, hemolytic disease of the newborn, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

- G6PD deficiency typically has an X-linked inheritance primarily affecting males; however, there are several inheritance patterns that can affect females.
- G6PD in conjunction with Gilbert *UDPGT1* genotype has a 3- to 5-fold increased risk of hyperbilirubinemia.
- Neonatal alloimmune thrombocytopenia is a platelet issue but can be precipitated by high AB antigen expression and ABO incompatibility. Double-volume exchange transfusion can rapidly decrease the circulating bilirubin level, but has potential for significant morbidity. Other options in the absence of neurologic signs of bilirubin encephalopathy are intravenous immunoglobulin G, fluid resuscitation, and aggressive phototherapy.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the differential diagnosis and evaluation of infants with indirect hyperbilirubinemia.

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2 Feeding Intolerance Following Topical Atropine Instillation in a Premature Infant

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AUTHOR DISCLOSURE Drs Lanlokun, Capriolo, Alexander, and Sundararajan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An extremely low-birthweight female newborn, weighing 545 g, is born at 23 weeks of gestation via cesarean section. Following a pregnancy complicated by preterm labor with prolonged rupture of membranes and positive maternal group B *Streptococcus* status, the newborn requires positive pressure ventilation, chest compressions, intubation, and surfactant administration in the delivery room. After initial stabilization, she is admitted to the NICU. She receives continuous positive pressure ventilation on day 37 after birth and is ultimately weaned to room air. She initially receives enteral feeds with breast milk and gradually advances to full enteral feeds by day 40 after birth. Within a week of tolerating full enteral feeds, she makes a transition to 24 kcal/oz of formula because of insufficient maternal breast milk supply. Her eyes are regularly screened for retinopathy of prematurity (ROP) from 31 weeks' postmenstrual age (PMA). Before each ROP screening, she receives cyclopentolate/phenylephrine and proparacaine ophthalmic eye drops. Her initial eye examination reveals bilateral zone 1 stage 1 ROP. After the diagnosis of bilateral zone 2 stage 3 ROP with plus disease is made at PMA of 36 weeks, she is successfully treated with laser ablation therapy to the peripheral avascular retina of both eyes after a brief period of having nothing orally for 4 hours. Her enteral feeds are resumed later on the same day after laser surgery. She is subsequently started on daily ophthalmic 0.5% atropine drops and tobramycin/dexamethasone ophthalmic drops 4 times a day. On postoperative day 1, she is noted to have tachycardia with pulses ranging from 190 to 200 beats/min 1 hour after ophthalmic atropine is applied. She continues to have intermittent tachycardia, but enteral feeds are continued as she continues to have normal physical examination findings.

DISCUSSION

Progression

On postoperative day 3 (94 days after birth), approximately 12 hours after the application of atropine ophthalmic drops, the infant developed hematochezia, increased abdominal distention, diffuse tenderness, and absent bowel sounds. Enteral feeds were discontinued, and she was started on intravenous fluids, intravenous piperacillin/tazobactam, and vancomycin therapy after drawing blood for bacterial blood culture, complete blood cell count, manual differential count, basic metabolic panel, and lactate. An initial abdominal radiograph reveals "mild diffuse gaseous distention of bowel" (Fig 1A).

A



Figure 1A. X-ray of the abdomen at the time of initial symptoms of abdomen distention and hematochezia

The differential diagnosis for this clinical presentation in a neonate includes, but is not limited to, infectious enterocolitis, neonatal appendicitis, cow milk protein allergy, food protein induced enterocolitis syndrome (FPIES), Hirschsprung disease, malrotation with obstruction, intestinal perforation, and late-onset neonatal sepsis. Neonatal appendicitis is extremely rare but can present with abdomen distention, and an abnormal bowel gas pattern on radiography. However, it would also be expected to show air-fluid levels. Allergic colitis including cow milk protein allergy or FPIES would be unlikely in a patient who had been previously tolerating feeds without other signs such as vomiting, diarrhea, and eosinophilia. Hirschsprung disease typically presents with a history of failure to pass meconium within the first 48 hours after birth in addition to the findings of abdominal distention, constipation, and feeding intolerance. Malrotation with obstruction, intestinal perforation, and neonatal sepsis can be associated with feeding intolerance, especially in a patient with hemodynamic instability.

Diagnosis

Abdominal radiography revealed pneumatosis intestinalis without evidence of free air or portal venous gas (Fig 1B). These findings, along with the clinical features of feeding intolerance, abdominal distention, and rectal bleeding, were consistent with the diagnosis of a necrotizing enterocolitis (NEC)-like illness. Ophthalmic atropine drops were then

B



Figure 1B. X-ray of the abdomen approximately 9 hours after onset of hematochezia. Black arrows highlight areas of pneumatosis intestinalis.

discontinued. The infant's laboratory findings remained reassuring without metabolic acidosis, thrombocytopenia, or dyselectrolytemia. Blood culture remained negative for bacterial growth. She completed an intravenous antibiotic

C



Figure 1C. X-ray of the abdomen following completion of treatment for NEC.

TABLE 1. Series of Cases of Patients Who Developed Necrotizing Enterocolitis or Paralytic Ileus after Topical Instillation or Oral Administration of Mydriatic Agents

AUTHOR; YEAR	TITLE OF CASE REPORT	MYDRIATIC DRUG ASSOCIATED WITH PARALYTIC ILEUS	POPULATION	SETTING	OUTCOMES / OBSERVATIONS
Baron-Janaillac et al; (1) 2011	Are mydriatic eye drops dangerous for pre-term infants?	Atropine	Preterm infant	ROP screening	A 6-week-old former 28 week gestation female died from NEC, shortly after receiving eye drops for screening for ROP.
Bauer et al; (2) 1973	Systemic cyclopentolate (Cyclogyl) toxicity in the newborn infant	Cyclopentolate	Premature twins	ROP screening	Both twins developed feeding intolerance, but one twin died from NEC complicated by an intestinal perforation.
Beatson; (3) 1982	Atropine and paralytic ileus	Atropine	Geriatric patient	Enteral atropine for treatment of sialorrhea	A 77-year-old male with Parkinson's disease developed paralytic ileus while being treated with oral atropine for sialorrhea.
Lim et al; (4) 2003	Transient paralytic ileus following the use of cyclopentolate-phenylephrine eye drops during screening for retinopathy of prematurity	Cyclopentolate-phenylephrine	Preterm infants	ROP screening	6-week old former 26 week and 25 week premature infants developed paralytic ileus within 8 hrs following topical cyclopentolate-phenylephrine administration.
Oyachi et al; (5) 2003	Development of ovine fetal ileal motility: Role of muscarinic receptor subtypes	Atropine	Animal model-bovine fetal gut	In vitro study of effects of bethanechol (muscarinic agonist) and antagonists (atropine) on ovine fetal GI muscle contractility	Anticholinergic effect of atropine on the ovine GI muscle was noted to be inhibitory in an age-dependent manner.
Ozgun et al; (6) 2014	Fatal necrotizing enterocolitis due to mydriatic eye drops	Cyclopentolate, tropicamide, phenylephrine	Preterm infant	ROP screening	4 hrs after administering mydriatic drops for ROP screening, a 6-week-old infant developed abdominal distention that progressed to surgical NEC and later died 24 hrs post-operatively.
Princelle et al; (7) 2013	Systemic adverse effects of topical ocular instillation of atropine in two children	Atropine	Pediatric patient	Emergency department	A 6-month-old male presented to the ED with acute onset of urinary retention lasting 36 hrs, after administration of atropine eye drops. A 2-year-old boy developed dry mouth, thirst, and drowsiness within 30 mins of receiving atropine eye drops.

course for 7 days, with significant improvement in her serial abdominal examination findings and radiologic resolution of pneumatosis intestinalis (Fig 1C) without surgical intervention. Enteral feeds were resumed after bowel rest and total parenteral nutrition for 7 days. She advanced to full-volume enteral feeds of 22 kcal/oz and transitioned to all oral feeds by 108 days of age.

The infant continued to receive cyclopentolate/phenylephrine and proparacaine ophthalmic drops for follow-up eye examination with neither vital sign changes nor clinical instability noted. Eye examination before discharge from the NICU showed zone 2 stage 0 bilateral ROP without plus disease. She continued to gain weight adequately and was discharged from the hospital at 117 days of age. Outpatient follow-up visits with pediatric ophthalmology confirmed continued resolution of ROP.

The Condition

NEC, a potentially devastating gastrointestinal emergency, and ROP, a preventable cause of blindness, are common morbidities affecting premature infants. Unlike pathogen-associated NEC, no specific definition exists for NEC-like illness associated with extreme prematurity and delayed feeding. NEC-like illnesses may be associated with intestinal immaturity, altered gut microbiota, delayed initiation or rapid advancement of enteral feeds. ROP has been associated with prematurity, low birthweight and hyperoxia states. In 1973, Bauer et al reported the sentinel case highlighting an association between increased systemic level of cyclopentolate used for ROP screening and a fatal case of surgical NEC. (2)

The use of atropine eye drops is thought to have played a role in the development of a NEC-like illness in our patient. Atropine is an anticholinergic drug often used as a mydriatic agent. Drainage of the drug via the nasolacrimal duct leads to systemic absorption and ultimately, decreased gastrointestinal (GI) tract peristalsis. Authors of prior case reports (Table 1) have hypothesized that premature infants are at risk of developing NEC from the adverse GI side effects of the mydriatic agent in addition to its effects on heart rate and blood pressure (8) and its half-life of approximately 13 to 38 hours. (1) Paralytic ileus has been described in association with atropine use in older patients as well. (3)

Oyachi et al evaluated the development of cholinergic receptors in the GI tract of sheep as a means of postulating the receptor subtypes present in neonates. (5) The study was based on the knowledge that muscarinic receptors play an important role in the physiology of the adult GI tract and that peristalsis is controlled by the parasympathetic and enteric nervous system. (5) An age-dependent increase in response

to the anticholinergic activity of atropine in neonatal (7 ± 1 day old lambs) GI tissue compared to that of the fetus was observed. The most notable effect was seen in the adult GI tract, suggesting possible age-dependent changes in receptor subtypes. One can, therefore, postulate that the later development of a NEC like illness in this previously hemodynamically stable infant who was tolerating full enteral feeds may have been affected by maturation of the GI tract, leading to increased sensitivity to the effects of atropine.

Ophthalmic atropine preparation is administered at a variety of concentrations ranging from 0.3% to 1%. (9) A reduction in the drop volume of cyclopentolate is associated with fewer adverse events, with a near equivalent effective pupil dilation. (10)(11) Withholding enteral feeds for 4 hours after ophthalmological examination, decreasing the drop size, and occlusion of the nasolacrimal system after instillation of mydriatic eye drops are some measures which could reduce the incidence of systemic absorption and resulting feeding intolerance. (12)(13)(14) There exists a significant knowledge gap in the literature regarding safety and pharmacokinetic data of topical atropine use in premature newborns that could be addressed with future research. Further study is warranted to characterize possible causation of a NEC like illness secondary to the systemic paralytic effects following topical atropine use.

Lessons for the Clinician

- It is important for the clinician to recognize unexplained tachycardia post-atropine instillation in a premature infant.
- Worsening vital signs and feeding intolerance can be observed as early as 24 hours after administration of atropine ophthalmic drops.
- After initial evaluation aimed at excluding infection, clinicians caring for neonates must be aware of systemic paralytic effects following topical atropine use.
- Neonates must be monitored for feeding intolerance and development of a NEC like illness following topical mydriatic application, both during the screening and following treatment for retinopathy of prematurity.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the differential diagnosis, diagnostic and laboratory features, and approach to management of infectious enteritis and colitis in the neonate.

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Index of Suspicion in the Nursery

1 Fever, Rash, and Hyperleukocytosis in a Newborn

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AUTHOR DISCLOSURE Drs Gupta, Anwar, Kirk, and Makker have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An infant is born at 38 weeks and 5 days' gestation via spontaneous vaginal delivery to a 22-year-old, gravida 2, para 1-0-1-1 woman. This pregnancy is complicated by preeclampsia and chorioamnionitis, and the mother is given magnesium sulfate, ampicillin, and gentamicin intrapartum. The mother has negative serologic findings for human immunodeficiency virus, hepatitis B, and syphilis. She is rubella immune and negative for group B *Streptococcus*. Membranes have been ruptured for 14 hours at the time of delivery. The neonate requires stimulation and oral suctioning at birth and has an Apgar score of 8 at 1 and 5 minutes. Immediately after birth, the neonate has a temperature of 102.9°F (39.3°C) and a diffuse nonblanching macular blue-purple rash. The neonate is admitted directly to the level 2 NICU.

Initial laboratory findings include a white blood cell (WBC) count of 167,200/ μ L (167.2×10^9 /L; 2% neutrophils, 1% basophils, 11% lymphocytes, 4% monocytes, and 82% blasts), hemoglobin of 18.3 g/dL (183 g/L), and platelet count of 142×10^3 / μ L (142×10^9 /L). The aspartate transaminase level is 118 IU/L (1.9 μ kat/L) and alanine transaminase level is 33 IU/L (0.5 μ kat/L). Prothrombin time is 31.7 seconds, partial thromboplastin time is 52.5 seconds, and fibrinogen is 116 mg/dL (3.4 μ mol/L). With attempts at intravenous line placement, fluid oozes from puncture sites. Fresh frozen plasma is administered while arrangements are made to transfer the infant to a tertiary care NICU.

DISCUSSION

Progression

Repeat laboratory tests at the tertiary care NICU showed a WBC count of 613,700/ μ L (613.7×10^9 /L; 19% neutrophils, 22% lymphocytes, 56% monocytes, 2% eosinophils, and 1% blasts), hemoglobin of 15.9 g/dL (159 g/L), and platelet count of 103×10^3 / μ L (103×10^9 /L). Cerebrospinal fluid obtained via lumbar puncture was clear with 8 WBCs (79% monocytes and 21% lymphocytes) and 21 red blood cells; glucose concentration was 54 mg/dL (3 mmol/L) and protein was 82 mg/dL. Urine and cerebrospinal fluid were tested for cytomegalovirus. Peripheral blood was tested for toxoplasmosis, Epstein-Barr virus, parvovirus, and rapid plasma reagin titer. After obtaining a blood culture specimen, the infant was started on empiric treatment with ampicillin and gentamicin.

Initial differential diagnoses included congenital leukemia and sepsis resulting in leukemoid reaction and/or disseminated intravascular coagulation. Infectious

disease and oncology specialists were consulted early in the infant's clinical course. The peripheral smear, which was reviewed by the pathologist, showed monocytes in many stages of maturation, raising the concern for leukemia. Peripheral blood specimen was sent for fluorescence in situ hybridization (FISH) panel for acute myelogenous leukemia (AML).

Diagnosis

Findings on the FISH panel for AML were abnormal, with 64% of cells expressing a rearrangement of the mixed lineage leukemia (*MLL*) gene. Given these results, a peripheral blood specimen was sent for flow cytometry, a bone marrow aspirate and biopsy were performed, and skin biopsy specimen of 1 of the remaining purpuric lesions was obtained. The flow cytometric analysis revealed an abnormal monocytic population, consistent with acute monocytic leukemia, which was supported by the bone marrow studies. The skin biopsy results were consistent with leukemia cutis. The infant was transferred to the oncology service to begin chemotherapy.

The Condition

Congenital, or neonatal, leukemia presents in the first 30 days after birth. It is responsible for fewer than 1% of all childhood leukemia cases and is found in approximately 1 in 5 million births. In the neonatal period, AML is more common than acute lymphocytic leukemia. AML has many subtypes, according to the French-American-British (FAB) classification system, with the most common in neonates being monocytic leukemia, FAB M5. Approximately 50% of all neonates with leukemia have an 11q23 translocation. This translocation affects the *MLL* gene, which is necessary for the proper production and differentiation of hematopoietic precursors.

Prenatal ultrasound findings are nonspecific and may include polyhydramnios, hydrops, and hepatosplenomegaly. The clinical signs and symptoms after birth are also nonspecific and many are secondary to anemia, thrombocytopenia, and/or neutropenia, if present. Newborns may have pallor, poor feeding, lethargy, hepatosplenomegaly, and/or oozing from puncture sites. Some may have respiratory distress, secondary to leukemic infiltration and/or pulmonary hemorrhage due to thrombocytopenia. Severe anemia may result in cardiac failure, thrombocytopenia may lead to intracranial hemorrhage, and leukocytosis can cause hyperviscosity and leukostasis.

The initial clinical finding is frequently leukemia cutis. Leukemia cutis is typically described as red, blue, or purple indurated nodules on any part of the skin. On initial appearance, it is commonly called a "blueberry muffin" rash. More than 50% of patients with congenital leukemia will have leukemia cutis and it occurs often in acute monocytic leukemia. When examined histologically, these lesions

contain immature cells that have infiltrated the dermis and the subcutaneous tissues.

The blueberry muffin rash can be found in other conditions. Congenital infections are known to cause this rash as well as leukocytosis and hepatosplenomegaly. Physical examination findings that can differentiate these infections from congenital leukemia include intrauterine growth restriction and microcephaly. Alternatively, a blueberry muffin rash may represent dermal erythropoiesis in infants with significant anemia. In times of increased demand, the neonate's skin can revert to its fetal function of hematopoiesis. If the anemia is secondary to hemolytic disease of the newborn, hepatosplenomegaly and thrombocytopenia may also be seen.

Another entity that can present with rash, anemia, thrombocytopenia, and hepatosplenomegaly is Langerhans cell histiocytosis (LCH), which is the second most common malignancy to present with cutaneous metastases in the neonate, after leukemia. Ultimately a skin biopsy will differentiate LCH from congenital leukemia. Transient myeloproliferative disorder (TMD) must also be considered in a newborn with leukocytosis, thrombocytopenia, hepatosplenomegaly, and blasts in the peripheral blood. TMD is associated with trisomy 21 and interestingly resolves on its own, earning the alternative name "transient congenital leukemia." TMD can be diagnosed with flow cytometry.

Infections, hemolytic disease, or hypoxia can result in leukemoid reaction. A leukemoid reaction can similarly present with leukocytosis, blasts in the peripheral blood, skin rash due to extramedullary hematopoiesis, and/or hepatosplenomegaly. However, the peripheral blood smear will not show a monoclonal cell population, and a bone marrow aspirate will show increased immature cells at various stages of maturation. It is important, but can be difficult, to rule out a leukemoid reaction.

Lessons for the Clinician

- Recognize the broad differential diagnosis for a "blueberry muffin" rash.
- Congenital leukemia is a rare but important cause of a "blueberry muffin" rash.
- Skin biopsies are rarely performed in neonates, but can confirm the diagnosis of congenital leukemia.
- It is important to rule out congenital infections in the evaluation of a patient with leukocytosis and rash.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical and laboratory features of congenital leukemia.

Suggested Readings

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- Childhood Cancer: <https://www.healthychildren.org/English/health-issues/conditions/cancer/Pages/Childhood-Cancer.aspx>
- Symptoms of Childhood Cancers: <https://www.healthychildren.org/English/health-issues/conditions/cancer/Pages/Symptoms-of-Childhood-Cancers.aspx>

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Index of Suspicion in the Nursery

2 Hematuria in a Preterm Neonate

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AUTHOR DISCLOSURE Drs Mahajan, Dummula, Wang, Raina, and Pandey have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 26-week-old female twin is born via cesarean delivery due to nonreassuring fetal heart tones noted in the 38-year-old mother. The pregnancy has been complicated by unequal placental sharing and velamentous cord insertion for this twin. Apgar scores are 2 and 7 at 1 and 5 minutes, respectively. Her birthweight is 25% lower than that of her twin.

Her clinical course is complicated by respiratory distress syndrome and pulmonary hypertension. On day 12 after birth, she develops fluid- and pressor-resistant hypotension secondary to fulminant sepsis. Notably, her international normalized ratio (INR) is 2.4 (normal, <1.1) and platelet count is $57 \times 10^3/\mu\text{L}$ ($57 \times 10^9/\text{L}$; normal range, $150\text{--}450 \times 10^3/\mu\text{L}$ [$150\text{--}450 \times 10^9/\text{L}$]). She proceeds to develop oliguria, which initially responds to fluids and diuretics. The following day, she becomes anuric, which is preceded by the passage of blood clots in the urine. Her blood urea nitrogen is 52 mg/dL (18.5 mmol/L; normal range, 7–20 mg/dL [2.5–7.1 mmol/L]) and creatinine concentration is 1.59 mg/dL (140.5 $\mu\text{mol/L}$; normal range, 0.8–1.2 mg/dL [70.7–106 $\mu\text{mol/L}$]).

Abdominal ultrasonography shows nonocclusive aortic thrombus with patent renal arteries and renal veins. Kidneys are normal in size without evidence of hydronephrosis (Fig, B). A large urinary bladder thrombus is visualized (Fig, A).

Urinary output is restored via placement of a catheter with improved renal function. Ultrasonography on day 15 shows the development of mild-to-moderate bilateral hydronephrosis as well as the known bladder thrombus and echogenic debris. On day 18, she slips back into anuria. Ultrasonography now reveals severe hydronephrosis (Fig, D) with an empty bladder that suggests proximal urinary tract obstruction (Fig, C).

DISCUSSION

Gross hematuria is an uncommon occurrence in the neonatal period. Although the true incidence is unknown, it is more frequently encountered in the sick preterm neonate. The most common cause of gross hematuria is renal vein thrombosis. Other causes include renal arterial thrombosis, coagulopathy, trauma, congenital anomalies including cystic kidney diseases, infections, nephrolithiasis, glomerulonephritis, and acute tubular/cortical necrosis. (1)

We believe this patient's gross hematuria was related to her sepsis. Laboratory results were positive for bacteremia as well as elevated C-reactive protein.

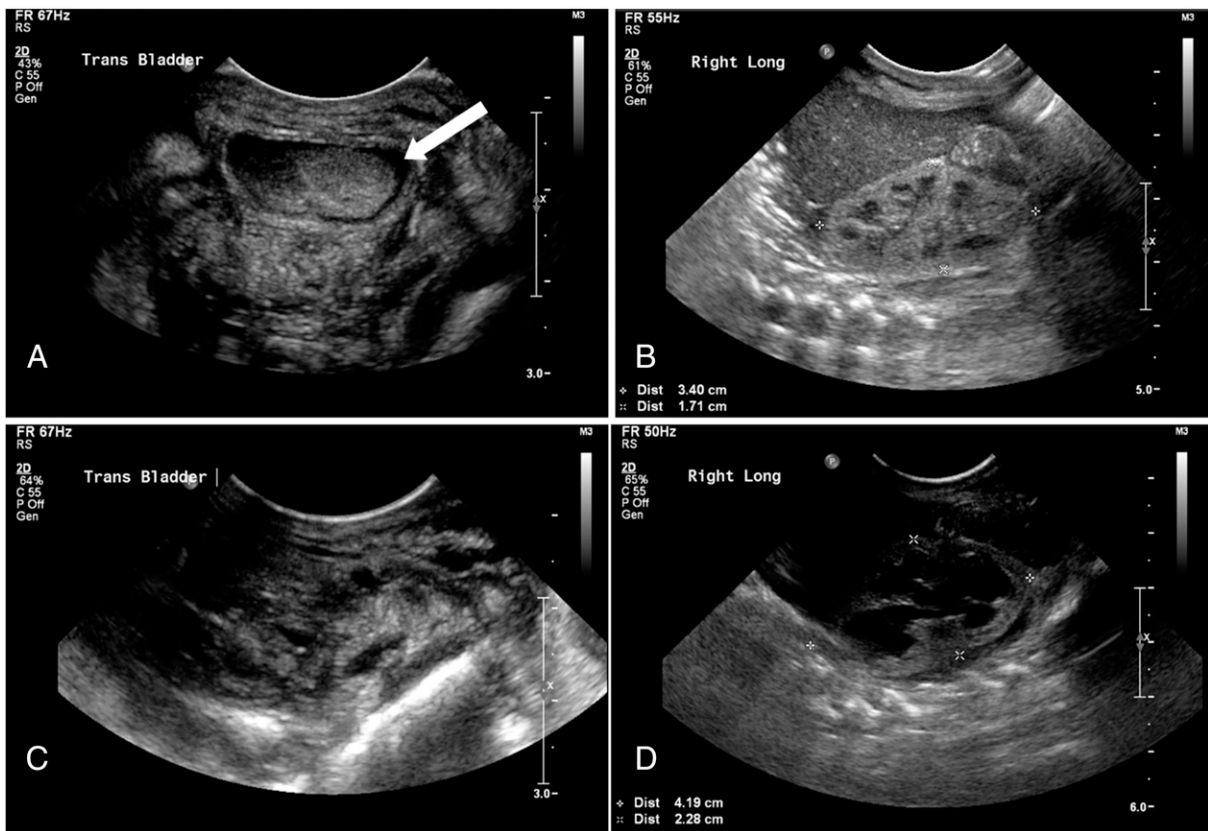


Figure. Upper panel (A and B) represents ultrasound images of bladder and right kidney on the day of initial presentation with gross hematuria. A large blood clot can be seen as an echodensity occupying the entire bladder (arrow in A). The architecture of the right kidney is well maintained at this time (B) but subsequent studies showed worsening hydronephrosis. Lower panel (C and D) represents images from a follow-up study conducted just before the nephrostomy tubes were placed. Decompressed bladder (C) and severe hydronephrosis (D) in the face of ongoing anuria were readily noted.

Blood cultures grew *Serratia marcescens*. Ultrasonography was negative for renal arterial and venous thrombi. This finding, which eliminated the most common cause of gross hematuria, coupled with her low platelet count and elevated INR suggest the presence of disseminated intravascular coagulation (DIC). Sepsis-induced DIC has been reported in the adult population but not in the neonatal population to the best of our knowledge. (2) This was further complicated by the development of intravesicular thrombus and subsequent obstructive hydronephrosis.

Although well described in both adults and older children, intravesicular thrombus is a rather uncommon phenomenon in the neonatal setting. (3) This uncommon occurrence carries a risk of bladder outflow obstruction as well as proximal urinary tract obstruction. Failure to identify an obstruction can lead to acute kidney injury, which carries a high mortality rate in this population. In addition, unrelieved obstruction can lead to chronic renal impairment, which is challenging to treat in the neonatal period

and beyond. (4)(5) Early recognition and monitoring of thrombi progression is key to improving mortality and morbidity in this patient population.

Currently, there is no standardized approach to the treatment and surveillance of obstructive clots in neonates. Our experience suggests that serial ultrasonography may be warranted throughout the duration of hematuria to avoid progressive renal damage caused by undiagnosed unilateral hydronephrosis. Unrelieved hydronephrosis increases the risk for chronic renal disease as well as increases mortality in the neonatal period. Proximal clots may require urologic intervention, thus making diligent surveillance much more important. Proximal obstruction may also be masked by compensation from the unaffected contralateral kidney. As seen in the current case, the neonate showed improvement of renal function and urinary output before slipping back into anuria secondary to severe hydronephrosis of the right kidney. This makes visual surveillance more important because laboratory values and urine output are not fully reliable in this situation.

The current patient had bilateral nephrostomy tube placement, which promptly improved renal function. The tubes were removed 6 days later, by which time adequate urethral flow was reestablished. The nonobstructive aortic thrombus, which was treated conservatively, resolved without the use of thrombolytics. At the time of this writing, the patient is 9 months old and has normal renal function with complete resolution of hydronephrosis. She is registering steady growth and achieving age-appropriate developmental milestones.

Lessons for the Clinician

- Gross hematuria may lead to bilateral or unilateral hydronephrosis by causing obstructive ureteropelvic junction clots.
- Untreated unilateral hydronephrosis may lead to permanent loss of renal functions.
- Signs of unilateral hydronephrosis may be masked by the presence of normal urine output and improving renal functions because of compensation from the unaffected kidney.
- Serial ultrasonography should be considered in cases of bladder thrombus or persistent hematuria to monitor for obstruction even with normal or improving kidney function.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Understand the treatment and complications of sepsis.

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Parent Resources from the AAP at HealthyChildren.org

- Blood in Urine (Hematuria): <https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Blood-in-Urine-Hematuria.aspx>

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Case 2: Hematuria in a Preterm Neonate

Chaitali Mahajan, Krishna Dummula, Joseph Wang, Rupesh Raina and Vishal Pandey

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Index of Suspicion in the Nursery

2 Herpes Simplex Virus Infection in a Preterm Infant and Complications

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AUTHOR DISCLOSURE Drs Kojima, Schein, and Karna have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

This preterm infant is the product of a dichorionic, diamniotic twin pregnancy born at 27 5/7 weeks' gestation to a 22-year-old woman via an emergency cesarean delivery for an abnormal fetal heartbeat. The woman's pregnancy was complicated with prolonged rupture of membranes 8 days before delivery, gestational diabetes mellitus, and a history of depression. She denies a history of sexually transmitted infections, including herpes simplex virus (HSV). She received ampicillin, amoxicillin, and azithromycin as well as 2 doses of betamethasone before delivery. The male infant has Apgar scores of 3, 4, and 8 at 1, 5, and 10 minutes after birth, respectively. An endotracheal tube is placed 4 minutes after birth, and the infant is admitted to the NICU.

He receives 1 dose of surfactant and is in stable condition with noninvasive ventilation. The infant receives ampicillin and gentamicin for 7 days for presumed sepsis. His complete blood cell count and C-reactive protein are within normal limits, with a negative initial blood culture. His screening head ultrasonography result is negative for intraventricular hemorrhage on day 7 after birth.

At 9 days of age, the infant develops respiratory distress and a diffuse vesicular rash on his axilla, neck, back, and chest. Cerebrospinal fluid (CSF) analysis reveals a white blood cell count of $54/\mu\text{L}$ ($0.5 \times 10^9/\text{L}$), red blood cell count of $4 \times 10^6/\mu\text{L}$ ($4 \times 10^{12}/\text{L}$), protein of 0.14 g/dL (1.4 g/L), and glucose of 63 mg/dL (3.5 mmol/L) with a simultaneous serum glucose concentration of 115 mg/dL (6.4 mmol/L). CSF, blood, and skin lesion test positive for HSV-2 via polymerase chain reaction (PCR). He is diagnosed as having disseminated HSV-2 infection with central nervous system (CNS) involvement and receives parenteral acyclovir for 21 days. His skin lesions gradually resolve, and the result of repeat CSF testing is negative.

Follow-up head ultrasonography at 28 days of age reveals a rare complication of HSV infection (Fig 1).

DISCUSSION

Progression

The routine screening head ultrasonography 28 days after birth shows bilateral thalamic hemorrhages and grade 1 intraventricular hemorrhage. Brain magnetic resonance imaging (MRI) with magnetic resonance angiography confirms the finding of bilateral thalamic hemorrhages (Fig 2) without evidence of sinovenous thrombosis. Evaluation for a clotting disorder is negative, and there are no clinical or electroencephalographic signs of seizure activity during

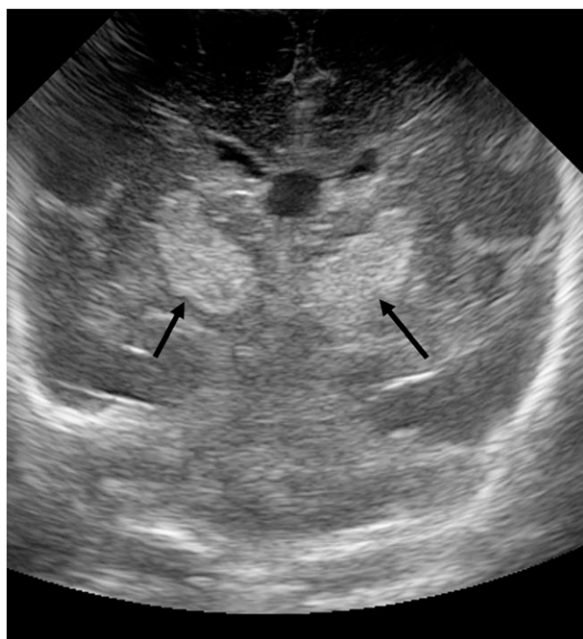


Figure 1. Head ultrasound 28 days after birth showing bilateral thalamic hemorrhage (arrows) and bilateral grade 1 intraventricular hemorrhage.

hospitalization. The infant is found to have bilateral glaucoma on routine ophthalmologic examination for retinopathy of prematurity. He is closely followed by the ophthalmologist.

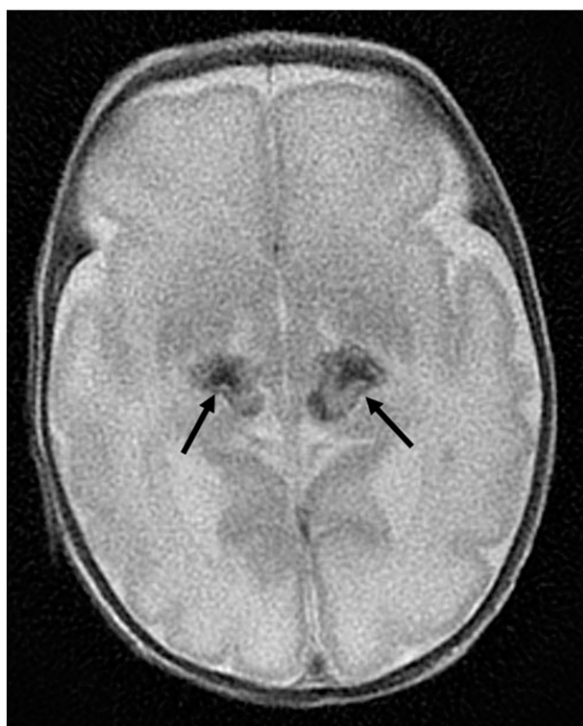


Figure 2. Brain magnetic resonance imaging scan (T2) 29 days after birth showing bilateral thalamic hemorrhage (arrows).

He suffers from severe laryngomalacia and gastroesophageal reflux, resulting in a tracheostomy, Nissen fundoplication, and gastrostomy tube placement. Multiple repeat head ultrasonographic images confirm improvement and resolution of both the thalamic and intraventricular hemorrhages by 8 months after birth.

The infant receives suppressive oral acyclovir after completing parenteral therapy. He has multiple outbreaks of cutaneous HSV lesions during his hospital stay despite suppressive therapy with acyclovir. After the third recurrence, acyclovir is switched to valacyclovir for improved oral absorption. He does not develop further cutaneous vesicles while being treated with valacyclovir. He is discharged from the hospital after 8 months in the hospital.

Condition

Incidence of neonatal HSV ranges from 1 in 3,000 to 1 in 20,000 live births. (1) Neonatal HSV infection is categorized into 3 types, depending on the extent of affected organ: disseminated disease involving multiple organs, localized CNS disease, and disease localized to the skin, eyes, and/or mouth (SEM disease). (1) Disseminated disease accounts for approximately 25% of neonatal HSV infections, (1) with mortality rates of 25% to 30% (1)(2) despite appropriate antiviral therapy. Long-term neurologic disabilities are noted in 13% of the infants who survive (3); these disabilities include cognitive abnormalities, speech disabilities, and attention-deficit/hyperactivity disorder.

Treatment of neonatal HSV infection is parenteral acyclovir, 60 mg/kg per day in 3 divided doses, regardless of the type or manifestation of the disease. Duration of intravenous treatment is 14 days for SEM disease and at least 21 days for CNS disease or disseminated disease. Infants with CNS involvement should have a negative result on HSV CSF PCR before discontinuing acyclovir. (1) After treatment of acute neonatal HSV infection, suppressive oral acyclovir therapy for 6 months improves neurodevelopmental outcomes. (4) Valacyclovir is an L-valyl ester of acyclovir that can achieve higher serum concentrations compared with oral acyclovir. Although oral valacyclovir may serve as an alternative for suppressive oral acyclovir, it has not been studied in cases of recurrent HSV infection resistant to acyclovir.

Brain MRI was found to be abnormal in 71.4% of infants with disseminated neonatal HSV infection with CNS involvement and thalamus abnormalities noted in 57.1%. (2) Bilateral thalamic hemorrhage was previously reported as a complication of HSV encephalitis (5) in term infants, but not in extremely low-birthweight (ELBW) infants. Thalamic hemorrhage and electroencephalographic (EEG) abnormality

have been reported as complications of cerebral sinovenous thrombosis, (6) but we did not find sinovenous thrombosis or EEG abnormality in our case. Other etiologic factors for neonatal hemorrhagic stroke include vascular malformation and coagulopathy. (7) Brain magnetic resonance angiography and coagulopathy studies were negative in the presenting case. It is difficult to ascertain that the bilateral thalamic hemorrhage in our case was secondary to HSV infection, especially with no previous report of bilateral thalamic hemorrhage in ELBW infants with HSV infection. However, we believe that this neonate's HSV infection contributed to the hemorrhage, given that neonatal HSV infection is known to be associated with thalamic abnormalities in term infants and that there were no other risk factors for hemorrhagic stroke in our case. It is important to have a thorough neuroimaging evaluation in case of disseminated HSV infection with CNS involvement and consider head ultrasonography if an MRI is difficult to obtain in a critically ill infant.

Lessons for the Clinician

- It is important to have a thorough neuroimaging evaluation in cases of central nervous system herpes simplex virus (HSV) infection.
- Treatment of neonatal HSV infection consists of parenteral acyclovir followed by suppressive oral acyclovir.
- Morbidity and mortality of disseminated neonatal HSV remains high despite therapy.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.

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Parent Resources from the AAP at HealthyChildren.org

- Herpes Simplex Virus (Cold Sores): <https://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Herpes-Simplex-Virus-Cold-Sores.aspx>

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

Case 2: Herpes Simplex Virus Infection in a Preterm Infant and Complications

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Index of Suspicion in the Nursery

3 Hydrops Fetalis, Pancytopenia, and Hemolytic Jaundice in a Preterm Neonate: A Diagnosis Made After 3 Months

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PRESENTATION

A 33-week-gestation female neonate with a birthweight of 1,920 g is born via vaginal delivery to a primigravida woman who is blood group A positive. She is referred to the NICU 1 hour after birth as a case of antenatally diagnosed hydrops fetalis.

Admission to 44 Hours After Birth

The newborn has stable vital signs with no respiratory distress or circulatory insufficiency. She is pale, with a distended abdomen, and tense on palpation. Ultrasonography reveals significant ascites with no pleural or pericardial effusion. A complete blood cell (CBC) count reveals anemia with a hematocrit of 30%. The total leukocyte count, absolute neutrophil count, and platelet count are within normal reference ranges for gestational age. Direct Coombs test (DCT) result is negative. A provisional diagnosis of hydrops fetalis with anemia is rendered, and congenital parvovirus infection is considered as a strong possibility.

44 to 96 Hours After Birth

The neonate develops indirect hyperbilirubinemia with a total serum bilirubin value of 15 mg/dL (256.5 μ mol/L) with a further drop in hematocrit to 26%. The CBC count reveals new-onset thrombocytopenia, with a platelet count of $50 \times 10^3/\mu$ L ($50 \times 10^9/L$), leukopenia with a total leukocyte count of $3,600/\mu$ L ($3.6 \times 10^9/L$), and neutropenia with an absolute neutrophil count of $800/\mu$ L ($0.80 \times 10^9/L$). The peripheral smear shows red blood cells (RBCs) with 12% reticulocytes, fragmented cells, spherocytes, target cells, and anisopoikilocytosis. Both white blood cells and platelets are also reduced in the peripheral smear. Results of both the DCT and the indirect Coombs test are negative. The neonate is treated with phototherapy, packed blood cell transfusion, and intravenous antibiotics for suspected sepsis. Septicemia or a nonimmune hemolytic disorder is strongly suspected.

96 Hours After Birth to Day 14

Phototherapy is stopped at 96 hours and restarted after 24 hours because of rebound hyperbilirubinemia and continued until day 8. Most of the blood reports are available. Blood culture report is sterile and antibiotics are stopped 48 hours after initiation. Glucose-6 phosphate dehydrogenase (G6PD) level is 19 U/g of hemoglobin, which is normal. Osmotic fragility for hereditary spherocytosis is normal and further testing is planned. Hereditary pyropoikilocytosis and elliptocytosis are ruled out based on the peripheral smear report. Tandem mass spectroscopy shows no abnormal results for galactosemia or other

AUTHOR DISCLOSURES Drs Ramaswamy, Rao, Suryanarayana, Darisi, and Gummadapu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

inborn errors of metabolism. Blood group incompatibility for Rh C, E, and Kell antigen is negative. Testing for toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH) infections is not suggestive. Blood tests for parvovirus immunoglobulin (Ig) M and DNA polymerase chain reaction (PCR) are negative. Urine testing for glycosaminoglycans for mucopolysaccharidosis is negative. Pancytopenia improves and all blood tests reach normal limits by day 14. The neonate is discharged by day 15 after birth. At the time of discharge, minimal ascites is present. The parents are advised to follow up with a plan for further evaluation for hereditary spherocytosis.

3 Months Post Natal Age

The infant's mother is admitted to an intensive care unit with fever, pallor, and thrombocytopenia. Her sensorium deteriorates and she receives mechanical ventilation. Neuroimaging reveals subdural hemorrhage. Her blood reports and bone marrow biopsy findings are consistent with systemic lupus erythematosus (SLE) with autoimmune hemolytic anemia and thrombocytopenia. The antinuclear antibody profile is strongly positive. Similar to the newborn, her DCT result is negative. Further testing, including DCT with RBCs washed with normal saline at 39.2°F (4°C) detects low-affinity IgG. The mother's sample, which had been stored at the time the infant was symptomatic, is positive for antinuclear antibodies. A retrospective diagnosis of neonatal lupus erythematosus with hydrops fetalis, pancytopenia, and hemolytic jaundice is made. At follow-up, the infant is growing well and developmentally normal. The CBC count repeated at age 3 months is normal, with no anemia, leukopenia, or thrombocytopenia. Ultrasonography of the abdomen reveals no ascites. The liver function test results are normal.

DISCUSSION

This was a case of neonatal lupus erythematosus that presented with immune hydrops fetalis with pancytopenia and hemolytic jaundice. Many of these mothers whose infants are affected are asymptomatic (~40%) and can develop manifestations of SLE later. (1) Neonatal lupus erythematosus can have varied presentations, from being asymptomatic in most cases to hematologic manifestations such as anemia, leukopenia, or thrombocytopenia to neonatal hepatitis or complete heart block. (1)(2)(3)(4) Cimaz et al, in a case series of 124 pregnancies with mothers affected with SLE, found the incidence of various hematologic abnormalities to be 27%. (5) Similar to our case, there are reports of neonatal lupus presenting without the classic skin rash or heart block.

The incidence of DCT-negative hemolytic anemia in the adult population is anywhere from 3% to 11%. (6) There

are many reasons for the DCT to be negative: 1) it could be because of the presence of IgG molecules on the RBCs at a lower density, which could not be identified by the commercial anti-IgG agent; or 2) it could be because of the presence of low-affinity IgG, which is removed while the RBCs are washed at 98.6°F (37°C). (6) The latter cause was responsible in the current case. The low-affinity IgG molecules were not specifically sought by washing the RBCs with cold saline at 4°C. Because the result of the DCT was negative, maternal SLE, which is a cause of autoimmune hemolytic anemia as well as pancytopenia in the newborn period, was not considered, and hence the diagnosis was missed. The low-affinity IgG coating the RBCs was detected in the mother at the time her general condition deteriorated. Her antinuclear antibodies were positive, thus confirming SLE. The blood samples of the mother, which were stored at the time of the infant's symptoms, tested positive for antinuclear antibodies, and the DCT conducted on the infant's RBCs revealed low-affinity IgG antibodies. Hence, a retrospective diagnosis of neonatal lupus erythematosus was made.

First Diagnosis

The presence of hydrops fetalis with anemia, with negative results on DCT pointed to a diagnosis of congenital parvovirus. However, DNA PCR for parvovirus was negative.

Second Diagnosis

The onset of pancytopenia with raised bilirubin level and negative results on DCT suggested an infective pathophysiology that could either be neonatal bacterial sepsis or TORCH infections. It could also be neonatal bacterial sepsis in an infant with an underlying condition predisposing for nonimmune hemolytic anemia (hereditary spherocytosis/elliptocytosis/pyropoikilocytosis), minor blood group incompatibility, G6PD deficiency. However, the tests for all of these conditions were negative.

Final Diagnosis

Clinical deterioration in the mother requiring intensive care unit admission and the subsequent diagnosis of SLE with immune hemolytic anemia and thrombocytopenia pointed to a similar autoimmune pathophysiology responsible for the development of hydrops fetalis with pancytopenia and immune hemolytic jaundice in the infant in the neonatal period. The blood tests were conclusive and a diagnosis of neonatal lupus erythematosus with immune hydrops and pancytopenia with hemolytic jaundice (caused by low affinity IgG) was made after a period of 3 months.

Lessons for the Clinician

- Neonatal lupus erythematosus should be considered in the differential diagnosis for immune hydrops fetalis.

- In the presence of a peripheral smear showing a hemolytic pattern, the possibility of an immune hemolytic anemia should be considered even when the DCT result is negative.
- Diagnosing an asymptomatic mother whose infant has neonatal lupus erythematosus might be life saving for the mother herself in the future.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes of and diagnostic approach to an infant who is anemic at birth.
- Know the etiology and pathophysiology of hemolytic anemias in the neonate.

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Case 3: Hydrops Fetalis, Pancytopenia, and Hemolytic Jaundice in a Preterm Neonate: A Diagnosis Made After 3 Months

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3 Hypermetabolic State in an Infant

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PRESENTATION

A 2,340-g male infant is born vaginally at 34 weeks of gestation to a mother with a history of asthma and hyperthyroidism. The pregnancy is overall uncomplicated except for preterm labor, and the delivery is notable for meconium-stained amniotic fluid and unknown group B *Streptococcus* status treated with 2 doses of penicillin. The infant does well initially with Apgar scores of 8 and 9, but soon develops tachycardia, tachypnea, and hypoxemia; radiography demonstrates respiratory distress syndrome with a small pneumothorax. Nasal cannula is needed to maintain normal oxygen saturations, and septic evaluation result is negative. Examination is notable for the vital signs described before, a barrel-shaped chest, and hyperreflexia. He is started on gavage feeds and treated with phototherapy for hyperbilirubinemia. On day 7 after birth, he suddenly develops worsening tachycardia to the 200s, tachypnea with respiratory distress, and decreased perfusion with mottling. Echocardiography reveals severe cardiac dysfunction, prompting transfer to the cardiac intensive care unit for stabilization. Laboratory results that day confirm the diagnosis.

DISCUSSION

Differential diagnosis for this neonate with tachycardia, tachypnea, and hypoxemia initially includes infectious diseases such as sepsis or viral infection; pulmonary diseases such as pneumothorax, congenital pneumonia, or meconium aspiration syndrome; cardiovascular diseases such as structural heart disease or arrhythmia, inborn errors of metabolism, hypovolemia, or anemia; and endocrine diseases such as hyperthyroidism. The infant's diagnosis was confirmed to be neonatal Graves disease when laboratory tests showed thyrotropin less than 0.005 mIU/L (normal 0.4–4.0 mIU/L), free thyroxine 5.73 ng/dL (74 pmol/L; normal 0.9–2.5 ng/dL [12–32 pmol/L]), triiodothyronine 3.34 ng/mL (0.05 nmol/L; normal 1.2–3.0 ng/mL [0.02–0.05 nmol/L]), and thyroid-stimulating immunoglobulin 240% (normal <130%).

Neonatal Graves disease is caused by transplacental passage of maternal stimulatory thyrotropin receptor antibodies. It typically presents within the first week after birth and is self-limited up to 3 months until the maternal antibodies disappear from the infant's circulation. Although neonatal thyrotoxicosis is most commonly seen in the setting of active maternal Graves disease, it can also occur in the context of treated maternal Graves disease, as in this case. Presenting symptoms for neonatal Graves disease include tachycardia, hyperthermia, hypertension, irritability, feeding difficulties, poor weight gain, goiter, prematurity and low birthweight, microcephaly, hepatosplenomegaly, heart failure, cholestasis, and exophthalmos. (1)

AUTHOR DISCLOSURES Drs Nair, Fu, and Haberman have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

First-line therapy includes an antithyroid medication such as methimazole and a β -adrenergic blocker such as propranolol. Propylthiouracil is avoided because of an association with liver failure. (2) Potassium iodide is added in refractory cases, and glucocorticoids can be used in extremely ill neonates. (1) If left untreated, neonatal hyperthyroidism can have dangerous long-term sequelae, including a mortality rate up to 25%. (3)

PATIENT COURSE

During his admission, the infant developed cachexia despite hyperphagia, conjugated hyperbilirubinemia (total bilirubin up to 28 mg/dL [479 μ mol/L] on day 12 after birth), and transaminitis (alanine aminotransferase up to 376 IU/L [6.3 μ kat/L] and aspartate aminotransferase up to 294 IU/L [4.9 μ kat/L]) on day 23 after birth. Potential infectious causes of conjugated hyperbilirubinemia were ruled out, and liver ultrasonography confirmed normal anatomy. Bilirubin levels declined as thyroid levels normalized. After extensive discussion among the primary, endocrine, and hepatology teams regarding the possibility of drug-induced liver injury, captopril was discontinued without any significant changes in transaminase levels. Methimazole was then halved and weaned, leading to a subsequent improvement in transaminase levels and normalization by age 2 months. Thyroid function results continued to normalize despite this medication adjustment. He has since been evaluated and treated for several issues including poor growth with advanced bone age, anaphylaxis, congenital hydrocephalus requiring ventriculoperitoneal shunt placement, and shunt-induced bicoronal craniosynostosis. He continues to work with multiple subspecialty teams to coordinate his care.

Lessons for the Clinician

- Although neonatal thyrotoxicosis is most commonly seen in the setting of active maternal Graves disease, it

can also occur in the context of treated maternal Graves disease. (1)

- Presenting symptoms for neonatal Graves disease include tachycardia, hyperthermia, hypertension, irritability, feeding difficulties, poor weight gain, goiter, prematurity and low birthweight, microcephaly, hepatosplenomegaly, heart failure, cholestasis, and exophthalmos. (1)
- First-line therapy includes an antithyroid medication such as methimazole and a β -adrenergic blocker such as propranolol. (2)
- Methimazole is known to cause liver injury and subsequent cholestasis, so hepatic function tests must be monitored carefully and therapeutic effects of such medications must be weighed against their capacity to cause liver injury. (2)
- If left untreated, neonatal hyperthyroidism can have dangerous long-term sequelae, including a mortality rate up to 25%. (3)

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Identify the etiology, clinical manifestations, laboratory features, and management of neonatal thyrotoxicosis.

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Case 3: Hypermetabolic State in an Infant

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Index of Suspicion in the Nursery

2 Infant with Early Direct Hyperbilirubinemia

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PRESENTATION

A female infant was born at 37 weeks, 1 day of gestation via cesarean delivery because of late decelerations. No resuscitation was needed, and Apgar scores of 8 and 9 were assigned. The mother reported receiving prenatal care, and her prenatal laboratory tests were positive for group B *Streptococcus* (GBS) carriage, and negative for gonococcus, hepatitis B, chlamydia, HIV, and rapid plasma reagin (RPR).

After the first round of breastfeeding, the neonate's abdominal girth increased from 33 to 35 cm, and she had visible jaundice without any rash. Laboratory results from an evaluation at 6 hours of age included the following:

- Complete blood cell count: White blood cells 12,500/ μ L (12.5×10^9 /L); neutrophils 55.1% (22% bands, 40% segmented neutrophils); platelet count 170×10^3 /uL (170×10^9 /L); hemoglobin 16.5 g/dL (165 g/L), and hematocrit 50%
- Chemistry: Total bilirubin 5.5 mg/dL (94 μ mol/L); direct bilirubin 2.5 mg/dL (43 μ mol/L); aspartate aminotransferase (AST) 58 U/L (0.97 μ kat/L); alanine aminotransferase (ALT) 17 U/L (0.28 μ kat/L); alkaline phosphatase 356 U/L (5.9 μ kat/L)
- C-reactive protein: 2.14 mg/dL (204 nmol/L)

She started treatment with intravenous ampicillin and gentamicin for presumed GBS infection. At 16 hours after birth, the C-reactive protein had increased to 7.34 mg/dL (699 nmol/L), and the total and direct bilirubin increased to 7.4 mg/dL (127 μ mol/L) and 3.6 mg/dL (62 μ mol/L), respectively.

On arrival at the NICU, she was active and in no distress in room air, with subtle dysmorphic facies, clear breaths, and no heart murmur, and her abdomen was full but not tense, without hepatomegaly. Laboratory findings on admission included an ALT of 12 U/L (0.2 μ kat/L), AST of 57 U/L (0.95 μ kat/L), and direct bilirubin of 4.0 mg/dL (68 μ mol/L).

DIFFERENTIAL DIAGNOSIS

- Biliary atresia
- Alagille syndrome
- Early-onset sepsis
- Hepatitis
- Congenital infections

CASE PROGRESSION

Abdominal ultrasonography demonstrated a contracted gall bladder with multiple echogenic foci, which could represent gallstones, and a normal common bile duct.

AUTHOR DISCLOSURES Drs Kumbhat, Folkins, Hawksley, and Cohen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Hepatology consultation suggested that the conjugated hyperbilirubinemia was likely secondary to an extrahepatic biliary obstruction. Treatment with oral ursodiol was started at 10 mg/kg every 8 hours.

Genetics was consulted for her subtle dysmorphic features, which included a flattened nasal bridge, prominent creases under the eyes, and tented lip. Echocardiography and eye examination, conducted as a part of the genetic evaluation, showed normal findings. Chest radiography performed for placing a peripherally inserted central catheter showed a hemivertebra at T-6. Conjugated hyperbilirubinemia and hemivertebrae are 2 of the 5 clinical diagnostic criteria for Alagille syndrome. (1) *JAG1* and *NOTCH2* sequencing and deletion/duplication analysis were performed (Prevention Genetics, Marshfield, WI), results of which were negative.

An evaluation for infectious diseases included a lumbar puncture with normal cerebrospinal fluid (CSF) studies. Polymerase chain reaction for blood and CSF was negative for enterovirus and herpes virus DNA, and surface viral cultures were negative. Urine cytomegalovirus result was negative. Blood cultures were negative. On the 4th day after birth, the pathologist noted that the placenta and umbilical cord showed necrotizing phlebitis without chorioamnionitis, concerning for a congenital infection, specifically congenital syphilis.

The placenta weighed 611 g, which is in the 90th to 95th percentile for a gestational age of 37 weeks. Microscopic examination (Fig 1) demonstrated necrotizing umbilical vasculitis and funisitis. The inflammatory infiltrate in the umbilical cord was

composed of mixed acute and chronic inflammatory cells, including plasma cells. The villi demonstrated patchy nonspecific villous edema but were otherwise unremarkable. No evidence was found to suggest an ascending chorioamnionitis. Both a Warthin-Starry stain and an immunohistochemical stain for spirochetes showed rare, small corkscrew-shaped spirochete organisms in the umbilical cord. The placental pathology was consistent with congenital syphilis.

Based on these findings, RPR titers and CSF VDRL tests were performed. The RPR test result was positive at 1:1,024, and CSF VDRL was positive at 1:8, consistent with congenital syphilis. Her skeletal survey showed fraying of multiple metastases with periosteal reaction along the long bones, consistent with congenital syphilis (Fig 2).

Ampicillin and gentamicin were discontinued, and the neonate was given a 10-day course of penicillin 50,000 μ /kg. Both parents retested positive for syphilis serology subsequently. Infectious disease, genetics, and gastroenterology followed up the infant after discharge. On her most recent gastroenterology follow-up, her γ -glutamyltransferase and direct bilirubin levels were normal, and ursodiol was discontinued.

DISCUSSION

Hepatosplenomegaly is a common presentation for congenital syphilis, but isolated direct hyperbilirubinemia is not. Cholestasis often is a nonspecific response to any systemic stress, resulting in a self-limiting “idiopathic neonatal hepatitis.”

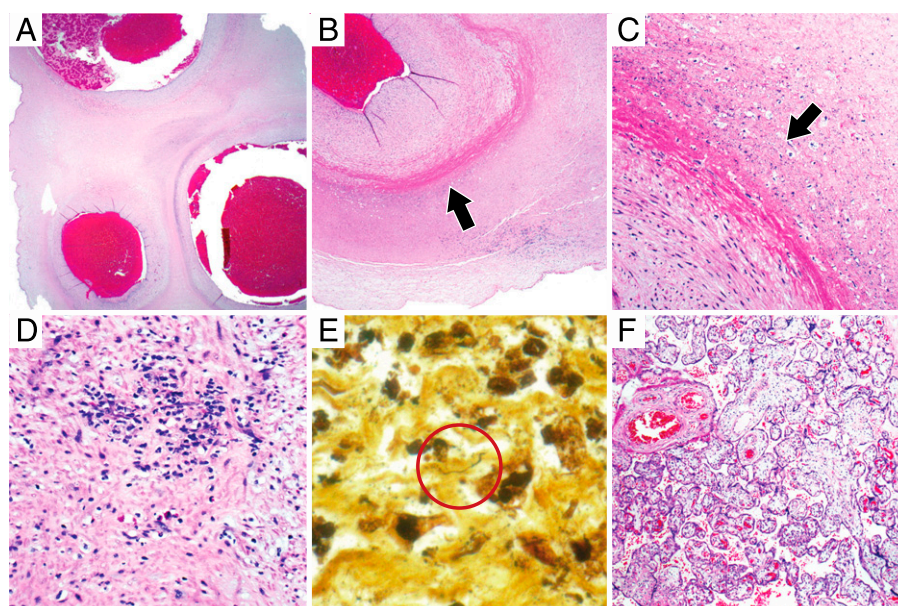


Figure 1. Microscopic pictures of the placenta. A. Low-power image of umbilical cord with rings of necrosis surrounding the umbilical vessels (H&E, $\times 2$). B. Closer image of necrosis (black arrow) around the umbilical vessel (H&E, $\times 4$). C. Necrotic debris (black arrow) in the Wharton jelly around the umbilical vessel (H&E, $\times 20$). D. Predominantly chronic inflammatory cells in the Wharton jelly of the cord (H&E, $\times 40$). E. Spirochete organism (black spiral in red circle) (Warthin-Starry, $\times 60$, image cropped to show organism). F. Chorionic villi with edema (H&E, $\times 10$).

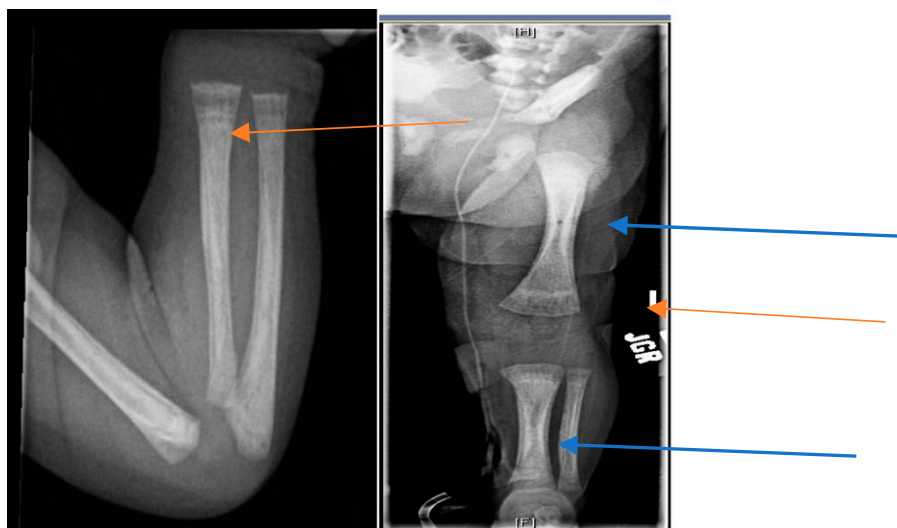


Figure 2. Metaphyseal changes (red arrows) and periosteal changes (blue arrows) in long bones.

However, it might be a presenting sign of serious infectious or metabolic disease (20%) or anomalies of the biliary tract (25%). (2) Most of the infectious causes of cholestasis are viral, which only represent 5% of the cases of neonatal cholestasis.

In the current case, the infant had isolated direct hyperbilirubinemia without any other symptoms of congenital syphilis. The maternal prenatal laboratory values were not significant for syphilis. This directed us down the path of noninfectious causes of direct hyperbilirubinemia, for which the results were negative.

The screening algorithms for congenital syphilis recommended by the Centers for Disease Control and Prevention (CDC) include screening with serologies. Maternal treponemal and nontreponemal immunoglobulin G antibodies are transmitted transplacentally, which complicated the interpretation of neonatal serologic test results. Congenital syphilis cannot be ruled out if a neonate has a nonreactive treponemal and nontreponemal test. (3) This makes the diagnosis of syphilis in neonates challenging. In the current case, the placental pathology was crucial in guiding this infant's evaluation.

Congenital syphilis continues to remain a problem in spite of an available cure. (4)(5) During 2015-2016, the CDC reported that the rate of syphilis in women rose by 35.7%. The rate of reported congenital syphilis rose by 86.9% from 2012 to 2016. (2) Given the resurgence of congenital syphilis worldwide, clinicians need to keep this diagnosis in mind when presented with isolated direct hyperbilirubinemia in a newborn, even if maternal serology was negative early in gestation.

Lessons for the Clinician

- Isolated initial direct hyperbilirubinemia is an uncommon presentation of congenital syphilis.

- Given the resurgence of congenital syphilis worldwide, clinicians need to keep it in mind when presented with isolated direct hyperbilirubinemia.
- Placental pathology was crucial in guiding the evaluation for this infant; special stains are needed to identify treponemes.
- Consider the diagnosis of congenital syphilis even with negative maternal serology, especially if not repeated in the second trimester or at delivery.

Note: This case is based on an oral presentation by Drs Kumbhat, Folkins, and Cohen at the Western Society for Pediatric Research conference; January 27, 2018; Carmel, CA.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations and diagnostic features of perinatal infections with *Treponema pallidum*.

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Case 2: Infant with Early Direct Hyperbilirubinemia
Neha Kumbhat, Ann Folkins, Carlene Hawksley and Ronald Cohen
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Index of Suspicion in the Nursery

3 Infant with Stridor

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AUTHOR DISCLOSURE Dr Morgan has disclosed no financial relationships relevant to this article. Dr. Stein has disclosed he is on the speaker bureau of Getinge Group and Chiesi Inc. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 3.74-kg term male infant is delivered at an outlying hospital via primary cesarean section because of a maternal history of hip surgery after prolonged rupture of membranes. The mother is a 26-year-old gravida 3, para 0, blood type A positive woman who is rubella equivocal, hepatitis B antibody negative, group B *Streptococcus* negative, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* negative, rapid plasma reagin nonreactive, and human immunodeficiency virus negative. Rupture of membranes is unknown, but occurred at least 1 day before arrival. Significant finding at delivery includes thick, meconium-stained amniotic fluid. The infant's 1-minute Apgar score is 5. He has stridor and respiratory distress. The DeLee suction is used on the stomach, and continuous positive airway pressure is initiated. His 5-minute Apgar score improves to 7, and he makes a successful transition to oxygen by nasal cannula. Due to the prolonged rupture of membranes, meconium-stained amniotic fluid, and persistence of respiratory distress, a blood culture specimen is obtained and he starts empiric treatment with ampicillin and gentamicin.

He is transferred to the special care nursery, where he continues to have stridor at rest. The stridor worsens with agitation. Chest radiography shows pneumomediastinum and pneumothorax. Over the next few days he continues to require intermittent oxygen via nasal cannula to maintain his saturations above 90%. A dose of racemic epinephrine and then albuterol do not improve the stridor. He is able to feed up to 47 mL of breast milk or formula every 3 hours. Blood cultures remain negative, and he continues to receive gentamicin and ampicillin.

By day 5, there is still no improvement of the stridor so he is transferred to a level 3 NICU for further evaluation. Admission examination revealed a neonate with stridor with intercostal retractions and intermittent cyanosis. Both the original chest radiograph and a repeat anteroposterior and lateral chest radiograph are now read as normal.

DISCUSSION

Diagnosis

Pediatric pulmonology is consulted, and a flexible bronchoscopy is performed at the bedside. This reveals laryngomalacia with edema of arythenoids, distal tracheomalacia most significant at the carina and turnoff to right mainstem, and incomplete right choanal atresia. The pulmonologist also raises concerns for tracheal compression. Initial images from a barium swallow are suggestive of esophageal compression, but the study is not completed because of interval worsening of the neonate's respiratory status. He undergoes intubation for

respiratory failure. Pediatric cardiology is consulted, and result of echocardiography is suggestive of a double aortic arch (Fig 1). Computed tomography (CT) angiogram with 3-dimensional reconstruction confirms the diagnosis (Fig 2).

The Condition

Double aortic arch is a rare cause of stridor in infants. Congenital heart disease occurs in about 1% of neonates. (1) Vascular rings account for only 1% to 3% of congenital heart disease because they occur in about 1 in 10,000 births. (2) Although double aortic arches are rare, they remain an important element of the differential diagnosis of neonatal stridor. The mean age at diagnosis for vascular ring is 6 months, (3) so the average infant with a vascular ring typically encounters a physician several times before the diagnosis is made. For this reason, it is critical for pediatricians to be aware of this anomaly and entertain its possibility in the differential diagnosis of stridor.

A double aortic arch is the result of failure of regression of the right fourth aortic arch. (4) In normal embryologic development, the aortic arches begin as a set of 6 perfectly paired arches in the fourth week of embryogenesis. Over the next few weeks, these pairs form the great arteries through selective growth and regression. It is unknown what causes the fourth arch to fail to regress; however, a few genetic syndromes are associated with higher rates of vascular rings, including Coloboma of the eye, Heart defects, Atresia

of the choanae, Retardation of growth and development, and Ear abnormalities and deafness (CHARGE) syndrome, Down syndrome, and DiGeorge syndrome. (5)

The clinical presentation of children with vascular rings is often related to compression of the esophagus and/or trachea. This can include feeding difficulties, vomiting, stridor, or respiratory distress. Evaluation of neonates with stridor often proceeds in a stepwise manner similar to the case presented. (6) A chest radiograph is often obtained first, because it is a low-risk diagnostic modality that allows the clinician to evaluate the infant's chest for other causes of stridor. Flexible bronchoscopy, which can identify the anatomic location of the airway defect, is typically the next test. This allows for evaluation of other types of stridor, including subglottic stenosis, webs, airway hemangiomas, and vocal cord motion impairment. (7) In the case of an infant with double aortic arch, compression of the trachea can be noted on bronchoscopy, and, if pulsatile, increases the diagnostic suspicion for vascular ring. CT angiogram of the chest and echocardiography allow for confirmation of the diagnosis, as well as aid in planning definitive surgical correction. (8)

When the diagnosis of double aortic arch is made, it is important for the clinician to be aware of the associations that it has with other congenital anomalies. Approximately 50% of children with double aortic arch have another abnormality. The most common is a second cardiovascular lesion, including ventricular septal defect, tetralogy of Fallot,

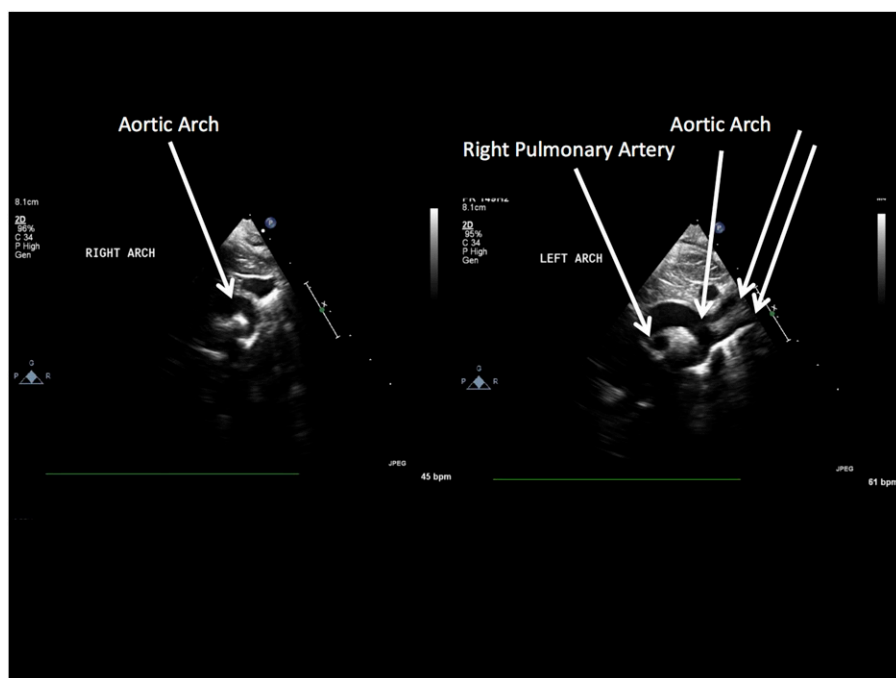


Figure 1. Echocardiogram of right and left aortic arches.

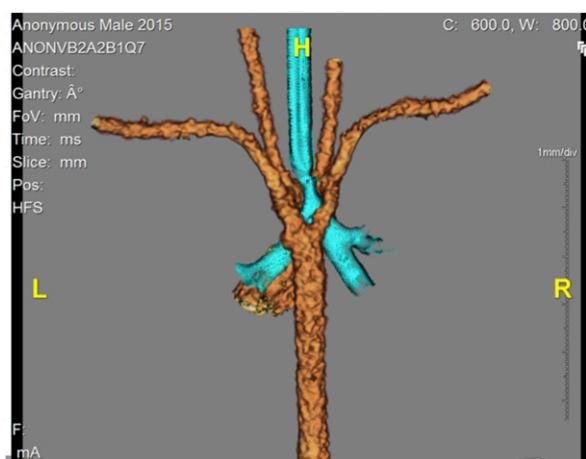


Figure 2. Computed tomography of the chest showing the paired aortic arches encircling the trachea.

or coarctation of the aorta. (7) Extracardiac lesions have also been reported, including cleft palate and subglottic stenosis. (8)

The definitive management modality for vascular ring is surgical correction. (4) In the case of double aortic arch, surgical ligation of one of the duplicated arches is indicated. This is performed through left thoracotomy, unless other cardiac malformations are also being corrected. (4) Often, sections of one of the aortic arches will be stenotic or atretic, which presents a natural site for surgical ligation.

Prognosis

Long-term outcomes for children with vascular rings are excellent. The procedure is associated with low surgical morbidity and mortality. (4) The most common postoperative finding is persistent tracheomalacia, which typically improves within the first 6 months. (3) Follow-up after the correction of vascular rings found that most children have some degree of persistent abnormality in their pulmonary function tests lasting into adolescence. (3)

Lessons for the Clinician

Infants with vascular rings can present with symptoms of feeding intolerance, stridor, or respiratory distress. The differential diagnosis for these complaints is wide and a step-wise approach to the evaluation will eliminate common

causes of feeding intolerance and respiratory distress and identify neonates with vascular anomalies.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the anatomy and pathophysiology (including genetics) of a neonate with an arterial vascular abnormality.
- Recognize the clinical features of a neonate with an arterial vascular abnormality.
- Recognize the laboratory, imaging, and other diagnostic features of a neonate with an arterial vascular abnormality.
- Formulate a differential diagnosis for a neonate with an arterial vascular abnormality.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a neonate with an arterial vascular abnormality.
- Know the various causes of stridor in the newborn and how to assess severity.

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Parent Resources from the AAP at HealthyChildren.org

- Severe Cases of Croup: When Your Child Needs Hospital Care: <https://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Severe-Cases-of-Croup.aspx>

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

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Index of Suspicion in the Nursery

1 Intramuscular Hematoma in a Neonate in the Nursery

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PRESENTATION

AUTHOR DISCLOSURE Drs Nanda, Thukral, and Nangia have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A very preterm (29 2/7 weeks) male infant with a birthweight of 998 g is delivered by lower segment cesarean delivery (for transverse presentation with spontaneous leaking). The mother is a 25-year-old gravida 2 woman with no history of consanguinity. There is a history of intrauterine death in a previous pregnancy (at 6 months of gestation) 2 years prior. The neonate does not cry after birth. The Apgar scores are 2 and 5 at 1 and 5 minutes, respectively. The neonate undergoes intubation and is transferred to the nursery for further management in view of ongoing poor respiratory efforts.

Clinical evaluation suggests multiple bruises over the left forearm, left leg, and right leg at birth. Early rescue (bovine) surfactant is administered 45 minutes after birth, ventilator settings are gradually lowered, and the neonate undergoes extubation and receives nasal continuous positive airway pressure (CPAP) 24 hours after birth. The neonate is given nothing by mouth for 24 hours, after which orogastric feeding is initiated (20 mL/kg per day) and then increased as per protocol. Treatment with caffeine (intravenous loading followed by oral) and vitamin A (injectable 5,000 IU alternate days, 3 days a week) is initiated.

Respiratory distress worsens 72 hours after birth, requiring increased CPAP support. Radiologic evaluation suggests infiltrates in both the lung fields, and treatment with antibiotics (piperacillin and tazobactam with amikacin) is initiated. Respiratory distress gradually improves, antibiotics are stopped after 10 days, and the neonate is weaned to room air on day 12 after birth. The neonate regains his birthweight on day 18 after birth.

The neonate is breathing room air with no respiratory distress and receiving full gavage feeds (180 mL/kg per day) till day 21, when he has 4 episodes of apnea requiring bag and mask ventilation followed by reinitiation of CPAP. Evaluation for secondary causes of apnea suggests negative sepsis screening result (total leukocyte count 19,200/ μ L [19.2×10^9 /L], absolute neutrophil count of 6,400/ μ L [6.4×10^9 /L], micro-erythrocyte sedimentation rate decreasing 5 mm in the first hour, qualitative C-reactive protein negative, immature to total neutrophil ratio 0.11), normal blood glucose (68 mg/dL [3.7 mmol/L]), normal serum calcium (8.8 mg/dL [2.2 mmol/L]), and no suggestion of intraventricular hemorrhage. Chest radiography suggests bilateral homogenous haze (Fig 1). The clinical differential diagnosis includes late-onset sepsis with pneumonia and/or lung collapse, and treatment with antibiotics (piperacillin and tazobactam with amikacin) is started.



Figure 1. Bilateral pulmonary haze on day 21 after birth.

CPAP is continued for the next 72 hours and then gradually weaned. On day 25, the neonate is lethargic and pale and has a hematoma of 11.5 × 9.5 cm in size over the right thigh (Fig 2). Examination reveals a heart rate of 150 beats/min, respiratory rate of 50 breaths/min, capillary refill time of 2 seconds, temperature of 98.6°F (37°C), and oxygen saturation of 94% in room air. Physical examination findings are within normal limits, except for skin pallor and a hematoma of 11.5 × 9.5 cm in size over the anterolateral aspect of the right thigh. Other systemic examination findings are normal. The neonate receives packed red blood cell transfusion.



Figure 2. Hematoma over the anterolateral aspect of the right thigh.

DISCUSSION

Diagnosis

The infant's hemoglobin concentration is 5.5 g/dL (50 g/L), with a hematocrit of 16.8% (0.17), total leukocyte count of 15,700/ μ L (15.7×10^9 /L), and total platelet count of 180 × 10³/ μ L (180×10^9 /L)—all of which are within normal limits. The coagulation profile is abnormal, with normal prothrombin time (11.0 seconds) and a prolonged activated partial thromboplastin time (96 seconds versus a control value of 40.6 seconds). The activated partial thromboplastin time improves after the administration of normal pooled plasma in a 1:1 dilution (40.7 seconds). Factor VIII (FVIII) level is 1% of normal, suggestive of moderate FVIII deficiency.

The Condition

The reported incidence of hemophilia is around 1 in 5,000 to 7,000. Hemophilia A accounts for about 80% to 85% of the total number of hemophilia cases (1)(2) in which the defects occur in the gene responsible for the production of protein FVIII, whereas the defect in hemophilia B affects factor IX (FIX) production. The 2 conditions are not distinguishable clinically. Though hemophilia is generally an X-linked hereditary disorder, the incidence of spontaneous mutation is also high (nearly one-third of cases). (2)(3)

Mechanism

FVIII and FIX participate in the activation of factor X and together with phospholipid and calcium, they form the factor X-activating complex. The clot formation is delayed and the clot formed is friable and soft. FVIII and FIX do not cross the placenta, so bleeding manifestations in hemophilia may be present from birth or may also occur in the fetus. (2)

Clinical Presentation

The severity depends on the activity of the deficient factor in the plasma. Hundred percent activity is equivalent to 1 unit/mL of factor; normal values are from 50% to 150%. Severe hemophilia (<1% activity) presents in early life. Moderate hemophilia (1%–5% activity) presents occasionally with severe bleeding after an injury and at times with spontaneous bleeding. Mild hemophilia (>5% activity) may remain undiagnosed or may present with bleeding after injury or surgery. Very rarely, the bleeding in mild hemophilia may be severe. (2)

The clinical presentation in hemophilia can be broadly categorized as spontaneous (intracranial or extracranial hemorrhage, umbilical bleeding, gastrointestinal bleeding, and splenic hematoma) or iatrogenic bleeding. (4) Iatrogenic

bleeding is more common in the neonatal period and spontaneous bleeding occurs more commonly later in infancy. (5) Neonates with hemophilia commonly present with umbilical bleeding, intracranial or extracranial hemorrhage, intravenous site bleeding, and bleeding after circumcision. In a case series, Conway and Hilgartner (5) found that the incidence of intramuscular hematoma as an initial presenting sign was approximately 5.7% in the neonatal period and significantly higher (52.4%) in the postneonatal period. Kulkarni et al, (6) in prospective data, reported that the onset of a first bleeding episode was within the first 30 days after birth in 207 (52.5%) of 394 infants, with the most common occurrences of bleeding being after circumcision (47.9%), followed by intracranial and extracranial hemorrhage (19.4%). Bleeding after intramuscular injection was reported as the initial site of bleeding in 2.8% of cases. (6) The occurrence of pulmonary hemorrhage has also been described but the exact incidence is not known.

FVIII level may be normal or slightly elevated in the neonate compared with adult levels. However, FIX levels are significantly lower at birth compared with adult levels. Hence, it is possible to diagnose hemophilia in the neonatal period. In mild hemophilia, where factor level may be at the lower end of the normal range, a repeat factor assay at around 6 months of age would confirm the diagnosis. (7) Preterm infants have a low FIX level compared with term infants. (7)

Information regarding the pharmacokinetics of factor replacement therapy for neonates is limited. So the dosage commonly used in older children is used for neonates. Neonates, especially preterm neonates, may have reduced recovery and increased clearance of FVIII and hence might require higher doses. (8)

CASE PROGRESSION

The infant in the current case received packed red blood cell transfusion followed by fresh frozen plasma. The opinion of pediatric surgery was obtained. Magnesium sulfate was applied along with the dressing every day. The size of the hematoma gradually reduced over the next 10 days. The neonate was administered FVIII concentrate before immunization and was discharged 59 days after birth (corrected gestational age of 37 3/7 weeks). He receives regular follow-up care, and has not had any recurrence of bleeding or hematoma.

The case came into clinical attention after presentation of the intramuscular hematoma. Clues to an underlying bleeding diathesis were present from birth. First, the neonate had multiple bruises over the body from birth. Second, he developed multiple episodes of unexplained apnea 21 days

after birth, which were attributed to late-onset sepsis with pneumonia, which could also have been a manifestation of pulmonary hemorrhage (because the other markers of sepsis were negative).

Lessons for the Clinician

1. Bruises in the neonatal period, particularly after a non-traumatic delivery, prolonged bleeding, and muscular hematoma in the neonatal period should prompt further investigations for an underlying bleeding disorder.
2. Intramuscular hematoma, which is commonly a presenting feature in older children with hemophilia, can also present infrequently during the neonatal period, and its presence should prompt a thorough evaluation for underlying bleeding disorder in the newborn.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the inheritance patterns of the common factor deficiencies

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Debasish Nanda, Anu Thukral and Sushma Nangia

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Index of Suspicion in the Nursery

2 Is It Neonatal Purpura Fulminans?

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PRESENTATIONS

AUTHOR DISCLOSURE Drs Herzlich and Levy-Mendelovich have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Case 1

A term newborn is first examined immediately after birth because of a widespread skin lesion that looks like cavernous hemangioma on his trunk and limbs (Fig 1). He had been born in a spontaneous vaginal delivery at the 40th week of gestation, with a birthweight of 3,450 g and an Apgar score of 9 and 10 at 1 and 5 minutes, respectively. The mother is a gravida 6, para 2, and abortus 3. Because she has had 3 spontaneous abortions, she undergoes a hypercoagulability profile whose findings are normal. The infant has a complete blood cell count that is normal, and shows no evidence of thrombocytopenia. The cutaneous lesions on his limbs, left palm, left knee, and right ankle are observed to be worsening at the age of 28 hours, and the skin looks like purpura with the beginning of necrosis (Fig 2). At this point, the blood tests show an elevation in the international normalized ratio (INR; 2.65) and a decrease in fibrinogen (110.7 mg/dL [3.25 μ mol/L]), and he receives fresh frozen plasma (FFP). He is transferred to the hematology department in a tertiary hospital to monitor his clotting factors. The differential diagnosis includes sepsis, cutis marmorata telangiectasia congenital, and neonatal purpura fulminans. He is treated with heparin, FFP, and antibiotics. In spite of having received FFP for 24 hours, his protein C level is only 20% (normal values 80%–150%), and he is diagnosed as having protein C deficiency. Head computed tomographic angiography is performed to rule out vascular malformation and,



Figure 1. A and B. Case 1. Appearance of the chest immediately after birth.

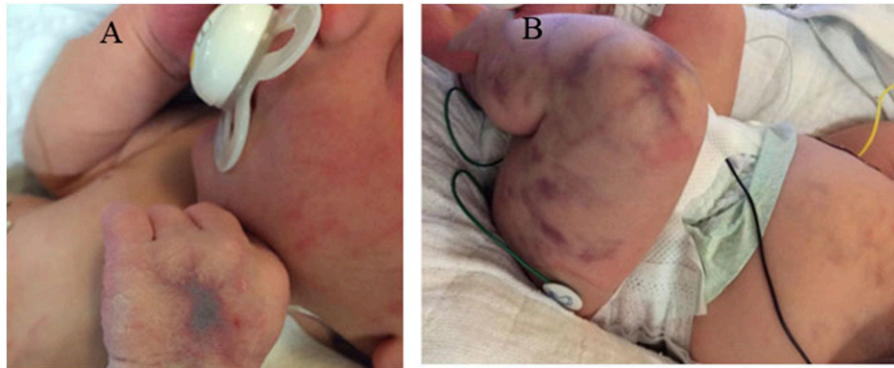


Figure 2. A and B. Case 1. Worsening of the lesions at 28 hours after birth.

although no malformation is found, a sinus vein thrombosis is suspected. No further changes in his condition are observed after 36 hours of additional monitoring in the PICU, and he is returned to the NICU with the recommendation to treat with low-molecular-weight (LMW) heparin twice daily and 1 unit of FFP once daily. The FFP is given as thrombolytic treatment for the skin areas with necrosis. On day 8 after receiving LMW heparin and FFP, protein C deficiency persists (30%), and the peak anti-Xa value is 0.48 (normal 0.3–0.8, therapeutic 0.5–1). The infant's condition remains stable, and on the 14th day of hospitalization, it is decided to stop the treatment with FFP though the protein C level is still low (36%). By the 18th day of hospitalization, the anti-Xa level is 0.66, and it is decided to discharge the infant and follow him at the hematology outpatient clinic. After 3.5 months of continuous LMW heparin treatment, he undergoes a head magnetic resonance imaging study, which rules out blood clots, malformations, and superficial vein thrombosis, whereupon the heparin treatment is stopped. Figure 3 demonstrates his condition at that time. Currently, the child is developing normally and the cutaneous manifestations are considerably faded.

Case 2

Five months after the first case, another newborn presents with similar manifestations of cutaneous discolorations. They had appeared on day 1 after birth as dark areas on the left knee. A management course of watchful waiting had been adopted, and at age 48 hours, the lesions are seen extending to the rest of the left leg (Fig 4) and to the back. At that point, a complete blood cell count, hypercoagulability profile, platelet count, and INR testing are conducted, results of which are all within normal range. The consulting hematologist advises prophylactic administration of 1 round of FFP and that the infant be transferred to a tertiary care PICU where he undergoes further observation and receives 1 injection of LMW heparin. When the clotting factors are

negative for a hypercoagulability state, he is finally diagnosed as having cutis marmorata telangiectasia congenita. No further treatment is administered, and he is discharged from the hospital after a few more days of observation, with the parents instructed to follow up at the pediatric outpatient department in 2 months. His prognosis is expected to be very good.

DISCUSSION

Neonatal purpura fulminans (NPF) is a dermal microvascular thrombosis associated with disseminated intravascular coagulation (DIC) occurring in the newborn period. (1) It may manifest as acute DIC and hemorrhagic necrosis of the skin, and the affected areas may eventually become necrotic and gangrenous, resulting in loss of the extremities. (2)(3)



Figure 3. Case 1. After 3.5 months of continuous low-molecular-weight heparin treatment.



Figure 4. Case 2. After 48 hours of age, on admission to the NICU.

NPF is a rare condition caused by congenital or acquired deficiencies of protein C or S, and one that is often fatal if it is not treated early and effectively. The clinical severity of NPF may vary, depending on the underlying cause. The onset of symptoms is usually within 2 to 12 hours after birth. (2)(4) The skin lesions initially appear dark red and then become purple-black and indurated, occurring at previous sites of trauma, such as intravenous cannula insertion sites. Protein C deficiency is often associated with thrombosis of the cerebral vasculature. (5) In contrast, cutis marmorata telangiectasia congenita is a rare, mostly benign, localized or generalized, vascular anomaly of unknown etiology characterized by persistent cutis marmorata, telangiectasia, and

phlebectasia. Diagnosis of cutis marmorata telangiectasia congenita is based on the clinical findings.

Lessons for the Clinician

- Dermal manifestations of an underlying disease/condition are unreliable for differential diagnosis.
- The detection of protein C deficiency confirmed a diagnosis of neonatal purpura fulminans in 1 newborn (requiring extended treatment), while the absence of abnormal laboratory results led to expectant management (no treatment) and uneventful course in another newborn diagnosed as having congenital cutis marmorata.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the cutaneous manifestations of neonatal hematologic disorders such as thrombocytopenia and coagulation disorders.

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Index of Suspicion in the Nursery

1 Late-Onset Hypoglycemia in an Extremely Low-Birthweight Infant

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AUTHOR DISCLOSURE Drs Ponnappakkam, Reeves, and Litke-Wager have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 800-g extremely low-birthweight female (25 5/7 weeks) twin A of a dichorionic-diamniotic gestation is born via primary low transverse cesarean delivery to a 37-year-old gravida 5, para 0-4-0-0 woman. The mother of the child is group B *Streptococcus* positive, and received 1 dose of penicillin less than 4 hours before delivery. Results of other antenatal testing had been reassuring. Preterm delivery is indicated for prolonged rupture of membranes of twin B, and the mother had received 2 doses of betamethasone 24 hours apart at the estimated 24th week of gestation.

The neonate has Apgar scores of 3 and 8 at 1 and 5 minutes, respectively. She is stabilized on continuous positive airway pressure and transferred to the NICU by 5 minutes after birth. In the NICU, she requires intubation and fraction of inspired oxygen greater than 60% to maintain oxygenation. An umbilical artery catheter and umbilical venous catheter are established and she is treated with ampicillin and gentamicin. She initially has hypotension requiring a 10-mL/kg bolus of normal saline without improvement, necessitating institution of a dopamine drip titrated from 2 to 5 μ g/kg per minute to maintain mean arterial pressures above 25 mm Hg. She is started on intravenous fluids of 100 mL/kg per day with a glucose infusion rate (GIR) of 5 mg/kg per minute, which is reduced to 3.1 mg/kg per minute by 1 day after birth because of worsening hyperglycemia. Despite serial reduction of GIR, she persistently demonstrates capillary blood glucose levels above 230 mg/dL (12.7 mmol/L). Thus, a 0.1 U/kg (0.08 U) dose of insulin is given intravenously. Shortly after the insulin administration, the NICU team is notified by the inpatient pharmacy that because of a dilutional error, the dose of insulin administered was 8 U, or 100 times the ordered dose.

DIFFERENTIAL DIAGNOSIS

Neurologic signs in the neonate such as jitteriness, lethargy, weak suck, and seizures should always prompt consideration of hypoglycemia as a cause. Though these signs are nonspecific, untreated hypoglycemia can have devastating consequences. In addition, diagnosis and treatment are relatively quick with few lasting side effects.

The differential diagnosis of hypoglycemia in the neonatal period is broad. In premature neonates who have not experienced the period of rapid glycogen accrual in late gestation, limited hepatic glycogen stores can lead to transient hypoglycemia. This can be further exacerbated by aberrant patterns of insulin secretion and distorted responses to blood glucose concentrations. Small-for-gestational age infants are also at increased risk for hypoglycemia because of inadequate substrate

for glycogen synthesis. Further, infants of multiple gestations may also be at risk for hypoglycemia because of relative placental insufficiency. The most common population to experience neonatal hypoglycemia is infants born to diabetic mothers. These neonates have increased secretion of insulin because of increased glucose concentrations in utero. After delivery, the neonate is no longer exposed to maternal hyperglycemia via placental transport, but increased insulin secretion can persist. This increased insulin secretion can cause decreased hepatic glucose production despite decreasing blood glucose levels due to the inhibitory effect of insulin on glycogenolysis and lipolysis. Increased peripheral utilization of glucose due to sepsis and inflammatory consumption is a common culprit causing glucose irregularity. Hypoglycemia that lasts for more than 5 to 7 days is uncommon and is more likely to be the result of congenital hyperinsulinism or inborn errors of metabolism. These disorders are rare and should be considered only after ruling out more common causes. In the setting of postnatal insulin administration, iatrogenic hyperinsulinism should also be considered.

THE CONDITION

Errors are common in the pediatric setting, and occur more commonly in the NICU than in other inpatient pediatric wards. Particularly in the NICU, many of these errors are medication related. Medication errors are defined as any mistakes that occur during the medication use process, including prescribing, dispensing, transcribing, administering, and monitoring. (1) In a sample of 1,230 reports of medical errors in 40 different NICUs, Suresh et al found that 47% of medical errors were medication errors. Of these medication errors, 25% were due to medication dispensing. (2) Rapidly changing weights, high acuity, and need for dilution all contribute to these higher rates of medication errors in the NICU. (3) Medications such as insulin, which must be serially diluted from stock solutions, further compound this risk and increase the potential for 10-fold and 100-fold errors. (4) The neonatal population is particularly susceptible to harm from medication errors because of their decreased physiologic reserve and inability to buffer harm. (5) However, in the largest available analysis of NICU errors, Stavroudis et al found that fewer than 5% of these medication errors lead to harm to the patient. (6)

MANAGEMENT AND CLINICAL PROGRESS

The infant was diagnosed with insulin overdose and the family was immediately notified. The goal of management

for insulin overdose is rapid correction of hypoglycemia and avoidance of future episodes. Thus, the neonate was given strict goal-directed therapies. First, 30-minute capillary blood glucose checks were instituted. If the screened glucose value registered less than 100 mg/dL (5.5 mmol/L), the GIR would be increased by 2 mg/kg per minute. If the glucose level became less than 80 mg/dL (4.4 mmol/L), the GIR would be increased by 2 mg/kg per minute, and a bolus of 200 mg/kg of 10% dextrose and water (2 mL/kg of D10W) would be administered. If the glucose level became less than 50 mg/dL (2.7 mmol/L), the GIR would be increased by 2 mg/kg per min and 4 mL/kg of D10W would be administered. Finally, if the glucose level became undetectable by capillary specimen, glucagon 0.2 mg/kg would be administered. Over the course of the next 3 hours, GIR was increased in a staggered fashion from 3.1 mg/kg per minute to a maximum of 10.6 mg/kg per minute with a glucose nadir of 95 mg/dL (5.2 mmol/L). The infant never required glucagon or a bolus of D10W and hypoglycemia resolved within 12 hours of the event.

This goal-directed therapy plan is supported by the literature on acute management of hyperinsulinemic hypoglycemia; administration of “miniboluses” of D10W in conjunction with an increase in GIR has been shown to normalize blood glucose concentration more rapidly than glucose infusion alone. (7)(8)

Lessons for the Clinician

- Hypoglycemia in the neonatal setting can have nonspecific signs and symptoms.
- Medication errors are common in the pediatric setting, and more common in the NICU.
- Medications such as insulin which require serial dilution are prone to 10-fold and 100-fold errors.
- Iatrogenic insulin overdose can be managed by increased glucose infusion rate in conjunction with the minibolus method.

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Note. The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the US Army Medical Department, the US

Army Office of the Surgeon General, the Department of the Air Force, the Department of the Army or the Department of Defense, or the US Government.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes.

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Index of Suspicion in the Nursery

1 Lethal Pulmonary Hemorrhage in a 3-day-old Term Infant

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PRESENTATION

A 38-1/7-week-gestation girl is born to a 21-year-old gravida 2, para 1 woman via normal spontaneous vaginal delivery. The woman had prenatal care with negative serologic findings. The infant is vigorous at birth with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. At approximately 30 hours after birth, she is hypothermic to 34.4°C with poor oral feeding, hypotonia, and tachypnea. Her glucose level is 32 mg/dL (1.78 mmol/L). A sepsis evaluation is performed, and ampicillin and gentamicin are started empirically. She is placed on high-flow nasal cannula for respiratory support and transferred to a nearby hospital for a higher level of care.

At approximately 34 hours after birth, the infant is noted to have coffee ground emesis, and she is in a clinical state of decompensation. She develops hepatomegaly, severe metabolic acidosis (base deficit -16), hyperkalemia (7.3 mEq/L [7.3 mmol/L]), and elevated creatinine concentration (1.52 mg/dL [134.4 μmol/L]). At approximately 45 hours, she develops bradycardia requiring intubation, chest compressions, and vasopressor support with 2 doses of epinephrine and initiation of a dopamine infusion. She is transferred to a tertiary referral center for further evaluation and management, given her continued clinical decline and severe metabolic derangements.

At approximately 49 hours after birth, she is noted to have hepatomegaly palpable to the level of the pelvis, delayed capillary refill, poor skin turgor, pale appearance, and hypotension. She has a potassium level of 7 mEq/L (7 mmol/L), and a rhythm strip shows ventricular tachycardia (Fig.). She is given calcium gluconate, nebulized albuterol, insulin, and dextrose containing fluids to address the hyperkalemia. Despite this, she has persistent stable ventricular tachycardia with blood pressures ranging from 50/30 to 70/50 mm Hg. In consultation with pediatric cardiology, intravenous lidocaine is started. Antibiotic coverage is broadened to ceftazidime, gentamicin, and acyclovir. She is found to have severe coagulopathy, with a prolonged prothrombin time of 61 seconds, international normalized ratio of 7.4, partial thromboplastin time of 93.3 seconds, and fibrinogen of 106 mg/dL (3.1 μmol/L). She remains severely acidotic (peak lactate >153 mg/dL (>17 mmol/L), base deficit of -24, and pH of 7.05) despite sodium bicarbonate boluses and a continuous infusion, as well as aggressive volume resuscitation with blood products. Her renal function worsens, with a peak creatinine concentration of 1.8 mg/dL (159 μmol/L) and elevated liver enzymes, including aspartate aminotransferase of 414 U/L (6.9 μkat/L), alanine aminotransferase of 84 U/L (1.4 μkat/L), and ammonia of 345 μg/dL (246 μmol/L). Because of concern for a metabolic disorder, additional studies are performed, with significantly abnormal α-fetoprotein of 76,800 ng/mL (76,800 μg/L)

AUTHOR DISCLOSURE Drs Schneider, DiBartolomeo, and Brennan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

and ferritin of 17,403 ng/mL (39,104 pmol/L). Pediatric hepatology is consulted, and intravenous immunoglobulin (IVIG) is initiated.

Because of a persistent coagulopathy, the infant receives continuous blood products, including 3 transfusions of fresh frozen plasma and 2 transfusions of cryoprecipitate. At approximately 60 hours after birth, bright red blood is noted coming from her endotracheal tube. With suctioning of the secretions, she develops bradycardia and experiences desaturation, which requires chest compressions. Copious and persistent bleeding is noted from the oropharynx and below the vocal cords upon visualization concerning for a pulmonary hemorrhage. After several doses of epinephrine, sodium bicarbonate, and calcium gluconate, there is no improvement in her cardiopulmonary status, and she dies approximately 1 hour later. The mother declines an autopsy.

Five days later, laboratory values show an elevated carnitine level of 47, acylcarnitine of 32, and abnormal newborn screening result.

DISCUSSION

The infant described herein has the severe lethal neonatal form of carnitine palmitoyl transferase (CPT) deficiency type II. CPT II deficiency is a rare inborn error of metabolism. CPTs are essential enzymes for energy production via beta-oxidation of long-chain fatty acids, a carnitine-dependent process. Three distinct clinical forms of CPT II

deficiency have been noted—the common benign adult form characterized by exercise intolerance and myoglobinuria, an infantile form with variable outcomes, and a lethal neonatal form. (1)

The first case of the lethal neonatal form of CPT II deficiency was described by Hug et al in 1989. (1) This form typically presents within the first few hours or days after birth and is universally fatal. It is characterized by liver failure, hypoketotic hypoglycemia, respiratory distress, cardiomyopathy, cardiac arrhythmias, seizures, and lethargy. (2) It also can include facial abnormalities and structural malformations of the kidney and brain. (3) The myocardium, liver, and skeletal muscle rely on beta-oxidation, and as such, CPT II defects are most pronounced in these organ systems. (4) Our patient's initial presentation of encephalopathy was secondary to impaired fatty acid oxidation leading to profound hypoglycemia. The most commonly reported causes of death in neonatal CPT II deficiency are cardiac arrhythmias, respiratory failure, renal failure, or cardiomyopathy. The current case is unique in that none of the reported cases in the literature identify severe coagulopathy resulting in pulmonary hemorrhage as the cause of death.

At the time of death, neonatal hemochromatosis/gestational alloimmune liver disease (GALD) was at the top of our differential. Neonatal hemochromatosis is a form of liver injury that results from transplacental transfer of maternal antibodies against fetal hepatocyte antigens. (5) It is characterized by iron accumulation in the liver and other tissues,

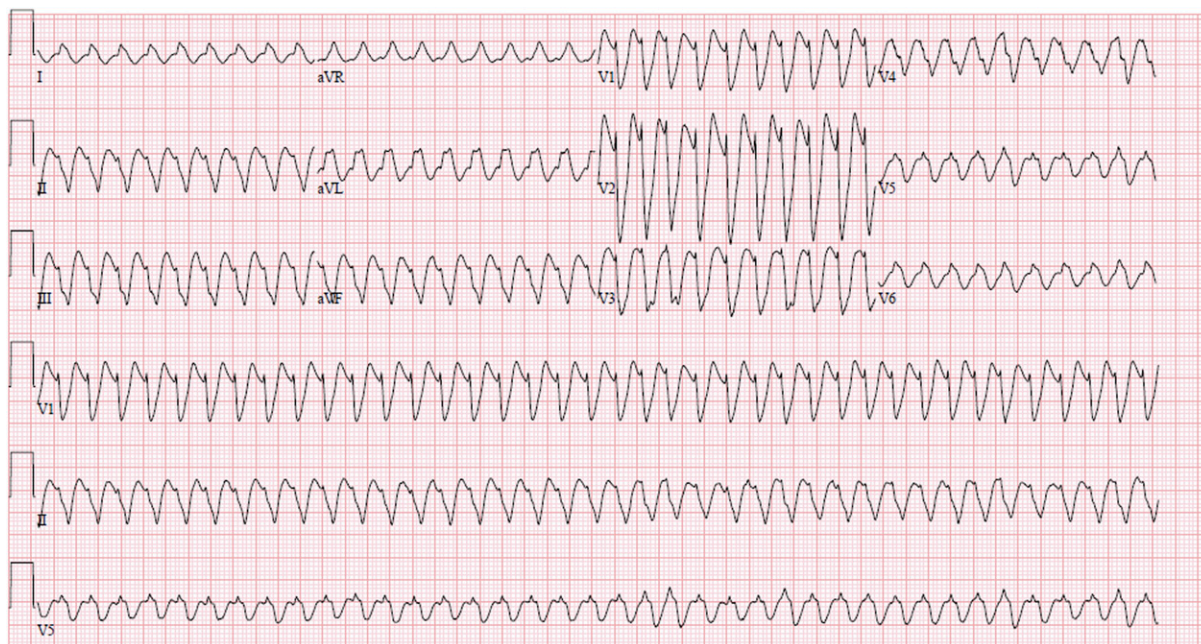


Figure. Rhythm strip with ventricular tachycardia.

resulting in hydrops, hepatomegaly, and ascites. Symptoms typically present in the first hours to days after birth with hypoglycemia, coagulopathy, hyperammonemia, hyperferitinemia, and elevated α -fetoprotein levels. Because of the presence of these symptoms in our patient, an IVIG infusion was initiated. This patient had additional clinical findings such as arrhythmias, seizures, and renal failure, which are not typically associated with neonatal hemochromatosis. However, any time a neonate presents with liver failure, neonatal hemochromatosis/GALD must be high on the differential. (5)(6)

Lessons for the Clinician

- CPT II deficiency is a rare inborn error of metabolism and can present in 3 forms—benign adult, variable infantile, and lethal neonatal.
- In neonates presenting with seizures, respiratory distress, cardiac dysrhythmias, liver failure, hypoglycemia, and unexplained coagulopathy, it is important to consider CPT II.
- The most commonly reported causes of death in neonatal CPT II deficiency are cardiac arrhythmias, respiratory failure, renal failure, or cardiomyopathy.
- CPT II shares common symptoms with neonatal hemochromatosis, so in any patient in whom liver failure and GALD is on the differential, IVIG therapy, which can be life-saving, should be initiated. (5)(6)

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids.

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Case 1: Lethal Pulmonary Hemorrhage in a 3-day-old Term Infant

Simone Schneider, Mara DiBartolomeo and Gillian Brennan

NeoReviews 2019;20:e737

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2 Metabolic Alkalosis in a Neonate 12 Hours after Birth

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AUTHOR DISCLOSURE Drs Tergestina, Chandran, and Kumar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant is born at 36 weeks of gestation with a birthweight of 1,780 g. The mother is not noted to have pregnancy-induced hypertension or gestational diabetes mellitus. Dating scan corresponds to the gestational age calculated from date of the last menstrual period. The anomaly scan is normal. A third scan notes that at a gestational age of 36 weeks, biparietal diameter corresponds to 34 weeks, femur length corresponds to 33 weeks, and the abdominal circumference corresponds to 28 weeks. Amniotic fluid index is 9 cm; umbilical artery Doppler images are normal. In view of the intrauterine growth restriction, 1 dose of steroids (betamethasone 12 mg) is given. Labor is induced; however, the cardiotocograph shows a basal heart rate of 150 beats/min, variability of 10 beats/min, no accelerations, and spontaneous decelerations to 100 beats/min, with recovery over 2 minutes. The infant is delivered via lower-segment cesarean with Apgar scores of 9 and 9 at 1 and 5 minutes after birth, respectively. In view of the low birthweight, the infant is transferred to the neonatal unit. Anthropometric measurements at birth are as follows: weight, 1,780 g (<3rd percentile); length, 44 cm (10th percentile); and head circumference, 31 cm (10th percentile). In view of the unexplained intrauterine growth restriction, it is planned to evaluate the infant for an intrauterine infection and he is started on expressed breast milk feeds via paladai (an Indian enteral feeding device).

At 12 hours after birth, the infant is noted to have an episode of apnea—cessation of breathing for approximately 30 seconds in association with desaturation. This recovers on stimulation. However, his breathing continues to be shallow and the respiratory rate is 30 to 40 breaths/min. Suspecting sepsis, a blood culture is performed and treatment with antibiotics (penicillin and gentamicin) is started. Chest radiography, echocardiography, and neurosonography findings are normal. An arterial blood gas measurement shows metabolic alkalosis, with a pH of 7.71, bicarbonate 43.4 mEq/L (43.4 mmol/L), and base excess +19.9 mmol/L. Partial pressure of arterial carbon dioxide (P_{aCO_2}) is 33.2 mm Hg (4.4 kPa).

DISCUSSION

Diagnosis

The blood gas measurement was repeated to confirm the presence of metabolic alkalosis. It was also reconfirmed that the infant had neither repeated episodes of vomiting nor multiple stools. The infant was also not receiving any medication. He passed urine twice in the preceding 12-hour period.

Investigations showed a sodium concentration of 133 mEq/L (133 mmol/L) and magnesium of 1.81 mEq/L (0.91 mmol/L). Serum potassium and chloride values were 2.9 mEq/L (2.9 mmol/L) and 85 mEq/L (85 mmol/L), respectively. There was no evidence of hypercalciuria, with a urine spot showing a calcium-creatinine ratio of 0.04. Urine pH was 8.38 and urine chloride was 11 mEq/L (11 mmol/L). Invasive blood pressure monitoring via radial arterial line showed pressures that were normal for gestational age. Ultrasonography of the kidneys and electrocardiography were performed, both of which had normal findings.

Maternal history included 4 admissions in the course of the pregnancy for hyperemesis gravidarum. Her history included approximately 20 episodes of vomiting per day. She was also evaluated by a gastroenterologist and surgeon for suspected subacute intestinal obstruction and pancreatitis, and by a psychiatrist for depression, psychosis, and an eating disorder; however, all evaluations were found to be negative. The mother was treated symptomatically with doxinate (doxylamine + pyridoxine hydrochloride tablet), ondansetron, and pantoprazole. The episodes of vomiting continued until delivery, with a 16-kg weight loss throughout the pregnancy. Maternal blood gas was measured at this point, and showed a pH of 7.6 and bicarbonate of 34.14 mEq/L (34.14 mmol/L).

Hospital Course

The infant was treated with normal saline boluses and potassium supplementation. His blood gas values normalized on day 4 after birth, and bicarbonate concentrations reached normal levels by day 5. Serum potassium was 3.3 mEq/L (3.3 mmol/L) at 48 hours after birth. Investigations for sepsis and intrauterine infections had negative findings. Feedings that were stopped on day 1 when the infant developed shallow breathing and apnea were restarted on day 2. Intravenous fluids were tapered as feeds increased, and were stopped on day 4. The infant started breastfeeding on day 4, and was discharged on exclusive breastfeeding.

The Condition

Metabolic alkalosis is characterized by a primary increase in serum bicarbonate concentration such as to increase the pH to more than 7.45. In the neonate, this is most commonly secondary to hydrogen ion (H⁺) losses as seen in vomiting/continuous nasogastric aspiration, congenital chloride-wasting diarrhea, renal losses such as Bartter syndrome, or endocrine causes such as congenital adrenal hyperplasia or hyperaldosteronism. Other causes of metabolic alkalosis are secondary to diuretic (loop or thiazide) administration or

inadvertent iatrogenic administration of bicarbonate or its sources. Metabolic alkalosis in the fetus is described secondary to excessive and prolonged vomiting and diarrhea and long-term administration of diuretics and prostaglandin E in the mother, leading to a hypochloremic metabolic alkalosis in the neonate. While the placenta acts as a clearinghouse for all metabolic disorders in the fetus, persistent alkalemia in the mother leads to increased transport of bicarbonate across the placenta, resulting in fetal alkalosis.

The physiologic effects of an elevated pH level are many. The respiratory drive can be inhibited via the central and peripheral chemoreceptors. This can present in the neonate as hypoventilation and apnea. Decreased myocardial contractility and arrhythmias and a secondary hypokalemia are well described. In the brain, alkalosis leads to cerebral vasoconstriction, and symptoms of lethargy and occasionally neuromuscular excitability and seizures.

Maternal weight loss secondary to hyperemesis gravidarum is described as a causative factor for intrauterine growth restriction. In addition to hyperemesis, long-term use of laxatives and diuretics and an eating disorder have also been described as causative for a pseudo-Bartter syndrome. The metabolic alkalosis, abnormal electrolytes, and weight loss in the mother in the current case resolved after delivery. The persistent maternal alkalosis led to a fetal metabolic alkalosis, which persisted after birth in the newborn.

Bartter syndrome is characterized by antenatal polyhydramnios, and postnatal features of a characteristic facies and hypokalemic metabolic alkalosis with increased urinary chloride excretion. The absence of the antenatal features, facies, and decreased urinary chloride levels differentiate this from Bartter syndrome. Aside from the classic history of recurrent gastrointestinal losses and metabolic alkalosis in the mother, the resolution of symptoms by days 4 to 5 also helped differentiate this from Bartter syndrome.

Historically, in 1979, infants fed with chloride-deficient soy formula developed hypochloremic metabolic alkalosis. Follow-up of these infants 9 and 10 years later found that their cognitive development appeared to be normal; however, these children were at risk of developing expressive language skill deficits. Follow-up of an infant with metabolic alkalosis in a mother with an eating disorder showed normal neurodevelopmental outcome at 2 years.

MANAGEMENT

The infant described here was treated with normal saline boluses given as infusions of 10 mL/kg. Potassium was added in the intravenous fluid at 3 mEq/kg per day. It was expected that restoration of effective arterial volume would

correct the chloride deficit and increase renal sodium bicarbonate excretion.

Reduced arterial blood volume leads to persistence of alkalosis as the kidneys conserve sodium, limiting the excretion of bicarbonate. Hypokalemia leads to increased proximal tubular bicarbonate reabsorption, and activation of hydrogen-potassium-adenosine phosphatase in the collecting tubules, which acts to reabsorb potassium in exchange for hydrogen ions. This leads to increased bicarbonate reabsorption and maintenance of the alkalemia. Supplementation of potassium leads to the intracellular movement of potassium in exchange for the movement of hydrogen ions into the extracellular fluid, which buffers the bicarbonate.

Lessons for the Clinician

- Metabolic alkalosis on day 1 in a neonate is usually secondary to a maternal cause.
- Treatment is via infusion of normal saline and supplementation of potassium chloride.
- Although the metabolic alkalosis resolves by days 4 to 5, long-term neurodevelopmental outcome is unknown.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.

Suggested Readings

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Index of Suspicion in the Nursery

1 Multiple Fractures at Birth

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AUTHOR DISCLOSURE Drs Gans, Underland, Levin, and LaTuga have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female neonate is born at 33 weeks of gestation via urgent cesarean section secondary to severe preeclampsia with hemolysis, elevated liver enzymes, and low platelet count syndrome. On examination, her weight is 1.18 kg (1st percentile), length 39.5 cm (5th percentile), and head circumference 27 cm (1st percentile). She is well appearing with white sclera, normal tone, and appropriate reflexes. She has scaphocephaly, a soft skull, proptosis with shallow orbits, low-set ears, swelling of the right wrist, a widened fontanelle, prominent knobs along her ribs, and frontal bossing. Laboratory results are notable for normal serum calcium, low serum phosphorous, elevated parathyroid hormone, low 25-hydroxy-vitamin D, elevated 1,25-dihydroxyvitamin D, normal urine electrolytes, and negative findings on New York State newborn screening (Table 1). Radiographs obtained shortly after birth show bony demineralization, metaphyseal flaring particularly at the wrists and knees, metaphyseal fractures, and bilateral rib fractures (Fig). The maternal history is significant for 5 previous miscarriages, nonadherence with taking prenatal vitamins, a diet containing minimal dairy products, and modest dress for religious observance, with limited skin exposure to natural sunlight. The parents are consanguineous.

DISCUSSION

The neonate is diagnosed with congenital rickets with secondary hyperparathyroidism complicated by in utero fractures, likely secondary to maternal vitamin D deficiency. Congenital rickets secondary to vitamin D deficiency is extremely rare with only 25 cases published to date. (1)

In humans, vitamin D₃ is synthesized after exposure to sunlight, metabolized in the liver to its storage form, 25-hydroxyvitamin D, and converted in the kidney by 1- α -hydroxylase to its active form, 1,25-dihydroxyvitamin D. 1,25-Dihydroxyvitamin D is primarily responsible for absorption of vitamin D and phosphorous in the gastrointestinal tract. Parathyroid hormone (PTH) increases serum calcium through bone reabsorption in addition to stimulating renal phosphorous excretion. In the setting of vitamin D deficiency, calcium cannot be absorbed through the gastrointestinal tract; maintenance of serum calcium is driven by PTH, which enhances calcium absorption from bone. (2) Veiled women who lack ultraviolet light exposure are at particularly high risk for vitamin D deficiency. (3) During pregnancy, vitamin D deficiency may be prevented by maternal sun exposure, dietary vitamin D intake, and prenatal vitamins. (4)

Congenital rickets secondary to maternal vitamin D deficiency from limited sun exposure and/or diminished oral intake causes bone disease in utero, which

TABLE 1. Initial Laboratory Testing

LABORATORY TEST	RESULT	REFERENCE
Phosphorous, mg/dL (mmol/L)	3.8 (1.2)	4-6.5 (1.3-2.1)
Calcium, mg/dL (mmol/L)	8.3 (2.08)	6.2-11 (1.5-2.7)
Parathyroid hormone, pg/mL (ng/L)	909.5 (909.5)	1-43 (1-43)
Alkaline phosphatase, U/L (μ kat/L)	1,038 (17.3)	63-483 (1.05-8.07)
25-hydroxyvitamin D, ng/mL (nmol/L)	14.3 (36)	>30 (>75)
1,25-dihydroxyvitamin D, pg/mL (pmol/L)	388 (1,009)	31-87 (81-226)
Urine phosphorous, mg/dL (mmol/L)	8 (2.6)	7-148 (2.2-47.8)
Urine calcium, mg/dL (mmol/L)	4.2 (1.05)	0.5-35.7 (0.13-9)
Urine creatinine, mg/dL (μ mol/L)	15.2 (1,344)	15-327 (1,326-28,907)
New York State Newborn Screening	Negative	Negative

can lead to fractures. These patients have low 25-hydroxyvitamin D with hyperparathyroidism, elevated alkaline phosphate, and decreased phosphorous. Characteristic findings of metaphyseal cupping on bone radiography may aid in diagnosis. (2) However, information on the minimum amount of vitamin D required for proper growth in the developing fetus and neonate is limited. Despite the lack of normative data for neonatal vitamin D requirements, this neonate's 25-dihydroxyvitamin D level was not as low as would have been expected in the setting of congenital rickets. We hypothesize that the patient's mother may have had increased vitamin D exposure toward the end of her pregnancy. The patient's clinical history and laboratory

findings are not consistent with other causes of rickets. Data regarding the long-term effects of in utero vitamin D deficiency on the development of the brain and other organs are limited.

Other causes of rickets include abnormal vitamin D metabolism from known genetic mutations, multiorgan failure, and inadequate intake or sun exposure, each with characteristic laboratory (Table 2) and clinical findings. In terms of mutations, pseudovitamin D deficiency rickets results from a mutation in 1- α -hydroxylase with subsequent low 1,25-dihydroxyvitamin D levels. These infants respond to 1,25-hydroxyvitamin D replacement. In hereditary vitamin D-resistant rickets, a mutation in the vitamin D receptor causes affected infants to have a limited

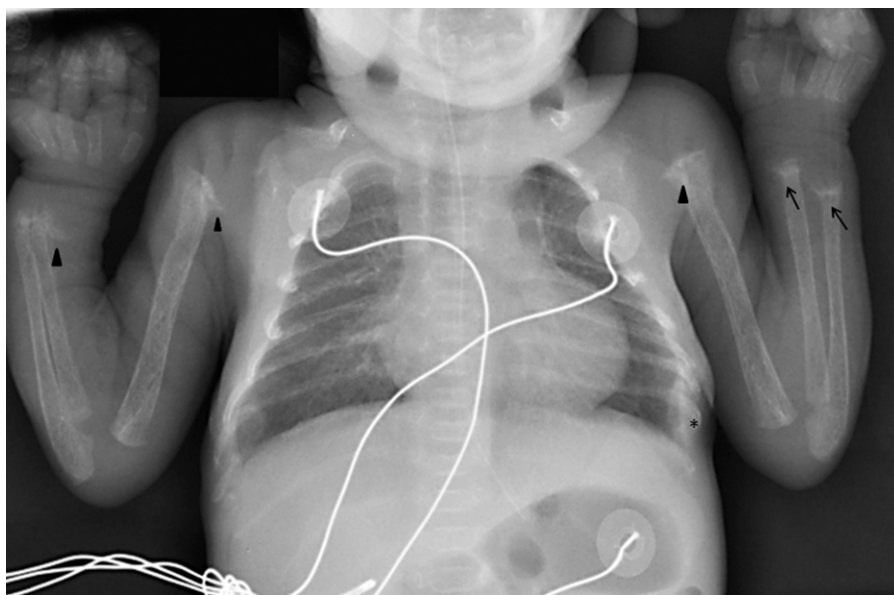


Figure. Frontal view of the chest demonstrates bone demineralization, flaring of the metaphyses at the wrist (arrows), and metaphyseal fractures (arrowheads). Bilateral rib fractures are noted (asterisk). Knee films demonstrated similar metaphyseal findings in the distal femora and proximal tibiae.

TABLE 2. Differential Diagnosis of Rickets in Infancy^a

DIAGNOSIS	SERUM CALCIUM	SERUM PHOSPHORUS	PARATHYROID HORMONE	25-HYDROXYVITAMIN D	1,25-DIHYDROXYVITAMIN D	ALKALINE PHOSPHATASE	URINE CALCIUM	URINE PHOSPHOROUS
Vitamin D deficient rickets	↓ NL	↓	↑	↓	↑ NL	↑	↓	↑
Pseudovitamin D deficiency rickets	↓ NL	↓	↑	NL	↑ NL		↓	↑
Hereditary vitamin D-resistant rickets	↓ NL	↓	↑	NL	↑↑	↑	↓	↑
Familial hypophosphatemic rickets	NL	↓↓	↓ NL	NL	↓	↑	↓	↑
Hereditary hypophosphatemic rickets with hypercalciuria	NL	↓↓	↓ NL	↓ NL	↑	↑	↑	↑
Renal osteodystrophy	↓ NL	↑	↑	NL	↓	↑	↓ NL	↓
Rickets of prematurity	NL	↓	↑ NL	NL	↑	↑	NL	NL
Oncogenic rickets	NL	↓	NL	NL	↑	↑	↓	↑

^aLaboratory findings compared with standardized values are normal limits (NL), elevated (↑), or decreased (↓).

response to high-dose calcium and vitamin D supplementation. Infants with familial hypophosphatemic rickets typically inherit an X-linked mutation affecting the PHEX protein, which inhibits renal phosphate absorption. These infants have decreased phosphate and 1,25-dihydroxyvitamin D without hyperparathyroidism, and 1,25-hydroxyvitamin D levels are replaced as treatment. In hereditary hypophosphatemic rickets with hypercalciuria, renal phosphate wasting causes an increase in 1,25-dihydroxyvitamin D levels and urine calcium excretion without hyperparathyroidism. These infants are treated exclusively with phosphate replacement.

Rickets may present as a component of renal osteodystrophy, which occurs in patients with chronic kidney disease when the damaged kidneys cannot convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and cannot excrete phosphate. This leads to secondary hyperparathyroidism and is managed with vitamin D replacement, phosphate binders, restriction of dietary phosphate, and dialysis. (2) Rickets of prematurity is most common among infants born weighing less than 1,500 g who have inadequate calcium and phosphate intake and requires replacement of minerals. (5) Lastly, paraneoplastic tumors can excrete substances that reduce renal phosphate absorption, leading to oncogenic rickets. Optimal treatment is tumor resection, but patients may also receive supplementation with phosphate and 1,25-dihydroxyvitamin D. (2)

MANAGEMENT

The neonate described herein was given calcium (25 mg/kg per day) and high-dose vitamin D (6,000 U) supplementation. Within a few weeks of supplementation, laboratory findings corrected and physical examination findings improved. The neonate's response to therapy supports the diagnosis of congenital rickets resulting from maternal vitamin D deficiency. The neonate was then transitioned to standard-dose vitamin D (400 U), calcium (12.5 mg/kg per day), and iron (4 mg/kg per day). The infant was fed 22 kcal/oz formula and discharged from the hospital at 39 weeks' corrected gestational age. The mother was given vitamin D supplementation and counseled regarding future pregnancies. The infant currently has gross motor delay at 12 months of age.

Lessons for the Clinician

- Etiology of rickets requires careful consideration of calcium, phosphorous, parathyroid hormone, and vitamin D values; clinical history; and response to therapy.
- Evaluation of a neonate with multiple fractures at birth should include a thorough maternal dietary history once other causes of fractures, such as nonaccidental trauma, have been excluded.

- Neonates born to mothers with modest dress for religious reasons with limited vitamin D supplementation during pregnancy are at risk for vitamin D-deficient rickets.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the interrelated effects of various hormones, including parathormone, calcitonin, and vitamin D on calcium, phosphorus, and magnesium metabolism in the fetus and neonate.

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American Academy of Pediatrics

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Index of Suspicion in the Nursery

1 Neck Swelling in a Neonate

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AUTHOR DISCLOSURE Drs Kim and Hoffner have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 32-day-old term African American male infant presents to the emergency department with a 1-day history of congestion and fussiness. The mother notes that his 2 siblings had a cold about 2 weeks ago, but she denies fever, cough, vomiting, diarrhea, and rashes. The infant has been breastfeeding without issues and has had a normal number of voids/stools. Earlier that morning, the infant had been taken to his pediatrician's office for his fussiness and was prescribed simethicone for possible gas-related symptoms. Later that afternoon, the infant's father had noted neck swelling on the right that spread toward the left side and he was brought to the emergency department.

His initial vital signs include a rectal temperature of 100.5°F (37.7°C), heart rate of 194 beats/min, respiratory rate of 46 breaths/min, oxygen saturation of 98% on room air, and a blood pressure of 98/50 mm Hg. The patient is well appearing and in no acute distress. His lungs are clear to auscultation, a II/VI systolic murmur is heard best at the left sternal border, and abdominal examination findings are normal. He has submental/neck fullness (right greater than left) with no erythema, warmth, masses, or fluctuance noted. No lymphadenopathy is appreciable on examination.

On further history taking, the mother states that the neonate was born at 38 weeks of gestation via uncomplicated vaginal delivery. She was group B *Streptococcus* (GBS) positive and had been inadequately treated. The neonate was observed after birth without antibiotics and was discharged from the hospital when vital signs and examination results were noted to be normal. In addition, prenatal ultrasonography had shown a "hole" in the heart, but because no murmur had been heard after birth, he did not undergo follow-up echocardiography. The patient has an appointment with cardiology next week.

In the emergency department, a full evaluation for sepsis is performed including blood, urine, and cerebrospinal fluid studies given the rectal temperature of up to 100.5°F (37.7°C) on presentation. The complete blood cell count shows a white blood cell (WBC) count of 11,700/μL (11.7 × 10⁹/L) with 61% neutrophils and 16% bands. Urinalysis shows 4 WBC per high power field, with a protein concentration of 0.03 g/dL (0.3 g/L) and glucose concentration greater than or equal to 500 mg/dL (27.7 mmol/L) with negative ketones. Cerebrospinal fluid studies show a WBC count of 3/μL and red blood cell count of 16/μL with a protein concentration of 0.04 g/dL (0.4 g/L) and glucose concentration of 99.0 mg/dL (5.5 mmol/L). The basic metabolic panel shows a glucose concentration of 162 mg/dL (9 mmol/L). Ultrasonography of the neck shows bilateral cervical adenopathy measuring 1.36 × 0.42 cm on the left and 1.32 × 0.68 cm on the right (Fig). No focal fluid collections are noted. The initial differential diagnosis includes infectious conditions such as abscesses and adenitis, congenital lesions such as thyroglossal duct cyst, and angioedema/allergy, as well as normal infant fat distribution.

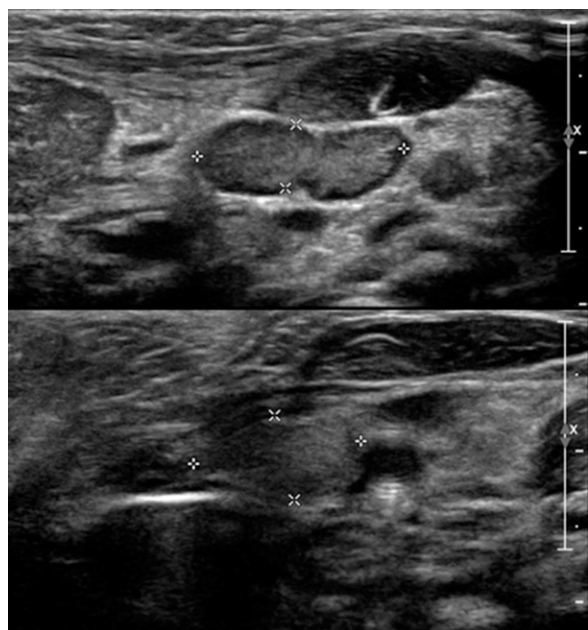


Figure. Ultrasonographic scan demonstrating prominent cervical lymph nodes.

The neonate is admitted to the pediatrics department and an ear-nose-throat specialist is consulted, who evaluates the patient and recommends coverage for infectious etiology without concern for congenital causes for neck swelling such as branchial cleft/thyroglossal duct cysts. An infectious disease specialist is consulted via telephone and recommends empirical coverage with clindamycin and ceftriaxone.

Within 12 hours of starting antibiotic therapy, the patient's neck swelling markedly improves, and the blood culture begins to grow gram-positive cocci in pairs/chains. As the swelling improves, lymphadenopathy is appreciable along the anterior cervical chain. Echocardiography shows a patent foramen ovale as opposed to atrial septal defect and bilateral pulmonary artery branch stenosis. Repeat urinalysis shows resolution of the glycosuria thought to be secondary to elevated serum glucose from stress. The fever resolves and the patient continues to eat, void, and pass stools as usual. The preliminary blood culture finding is positive for group B *Streptococcus agalactiae* sensitive to penicillin and the antibiotic treatment is narrowed to ampicillin. Repeat blood culture performed after the antibiotic course remains negative. Intravenous antibiotics are continued for 7 days and the patient makes a transition to oral amoxicillin for 3 more days for a total course of 10 days. The diagnosis of late-onset GBS bacteremia with cervical lymphadenitis is made.

DISCUSSION

In infants, GBS typically presents as early-onset disease (disease that presents before 7 days of age), late-onset disease

TABLE. Presentations of Group B *Streptococcus* (1)

Early-onset disease
• Bacteremia (most common at 80% to 85%)
• Pneumonia (10% to 15% of presentations)
• Meningitis (5% to 10% of presentations)
Late-onset disease
• Bacteremia (65% of presentations)
• Meningitis (25% to 30% of presentations)
• Other (pneumonia, cellulitis, osteoarticular infections)
Late-late onset disease
• Bacteremia

(up to 89 days after birth), and late-late onset disease (up to 6 months of age). (1) Early-onset disease is the most common, accounting for about 60% to 70% of all GBS disease. (2) Late-onset and late-late onset disease are less common. The types of presentations for GBS are shown in the Table.

For early-onset disease, the pathogenesis involves vertical transmission from the mother to neonate. Some theorize that bacteremia results from inhalation of infected amniotic fluid and/or genital secretions into the lungs, where the GBS β -hemolysin promotes lung epithelial cell invasion and then subsequent invasion into the blood. (3) However, the pathogenesis of late-onset disease is less well understood. Intrapartum antibiotic prophylaxis has shown to help prevent early-onset disease, but has had no effect on the incidence of late-onset disease. (4)

Late-onset disease is less common than early-onset disease. The current patient presented with adenitis, which is an even less common presentation of GBS. However, this case does fit the timeline for cellulitis and adenitis of late-onset disease, because the peak incidence is generally around 5 weeks of age and the condition has a male predominance. The drug of choice for treatment of proven GBS infections is penicillin. Length of treatment depends on the site of infection, ranging from 10 days for bacteremia without a focus to 4 weeks for osteomyelitis. (1)

Lessons for the Clinician

- The diagnosis of late-onset group B *Streptococcus* (GBS) infection should be considered in infants between 1 week and 3 months of age presenting with neck swelling.
- Antibiotic coverage should be broad on initial presentation, with narrowing within 24 to 48 hours once GBS and sensitivities are confirmed.
- Index of suspicion for invasive disease in neonates always needs to be high given that these infants can initially appear well.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of perinatal/neonatal group B streptococcal infections.
- Know the clinical manifestations and diagnostic criteria of group B streptococcal infections.

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Index of Suspicion in the Nursery

2 Neonate with an Eye Mask

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AUTHOR DISCLOSURE Drs Priyadarshi and Thukral have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant (weight 2,340 g) is born to a 39-year-old gravida 2 woman with previously diagnosed systemic lupus erythematosus and a history of 1 preterm intrauterine fetal demise, at 34 weeks of gestation. The mother had been taking oral steroids, azathioprine, and hydroxychloroquine for the last 14 years. She had positive antinuclear antibodies and anti-double-stranded DNA antibodies with biopsy-proven class III lupus nephritis, which worsened during pregnancy with increasing proteinuria. The pregnancy was terminated at 34 weeks through elective lower segment cesarean delivery. During pregnancy, the mother had regular antenatal follow-up visits and underwent investigations including maternal anti-Ro/La antibodies, which were negative, and fetal echocardiography, which had normal findings. At the time of birth, the infant is noted to have erythematous scaly thin plaques on his head, face, and neck (Fig 1). The differential diagnoses for these skin lesions include neonatal lupus, congenital rubella, congenital syphilis, and Bloom, Rothmund-Thomson, and Cockayne syndromes.

Postnatally, the infant is evaluated for other manifestations of neonatal lupus, which are normal including electrocardiography for heart block, hemogram for cytopenias, and liver function tests for hepatitis. In view of the maternal history and classic skin lesions (Fig 2), a diagnosis of neonatal lupus is made. The infant is



Figure 1. Confluent erythematous plaques around the eyes, giving an “owl eye” or “eye mask” appearance.



Figure 2. Close-up view of erythematous plaques on face and head.

discharged, with advice to avoid sunlight exposure and be exclusively breastfed after ensuring compatibility of maternal medications with lactation.

DISCUSSION

Neonatal lupus includes a characteristic rash (70%), typically affecting the face (especially the periorbital area), trunk and scalp, which can be erythematous macules, or papules which are rounded annular or elliptical in shape with erythema, and scaling sometimes covered with fine scales. (1) The rash is usually transient, may appear at birth but typically presents within first 6 weeks of age following sunlight exposure, and lasts 3–4 months. (2)

Other manifestations of neonatal lupus include cytopenias (10%) and hepatitis (10%), which are usually reversible, and congenital heart block (15–30%), which is permanent. (2)(3) Significant conduction abnormalities, detectable by echocardiogram in utero, may require cardiac pacing while transient manifestations are managed conservatively.

Skin rashes are amenable to avoidance of sunlight exposure and occasional use of topical steroids. (4)(5)

Lessons for the Clinician

- The confluent erythema around the eyes which gives a classic “owl eye” or “eye mask” appearance along with a history of lupus in the mother should clinch the diagnosis of neonatal lupus.
- Infants with cutaneous lesions of neonatal lupus pose a diagnostic challenge in the absence of maternal history. A high index of suspicion along with a good maternal history and maternal testing for autoantibodies can help make the diagnosis in such cases.
- In difficult situations, skin biopsy may provide a diagnostic clue. Findings on skin biopsy resemble the histopathological findings of subacute cutaneous lupus, with major features being keratinocyte damage and a superficial mononuclear cell infiltrate. (6)
- Any infant with neonatal cutaneous lupus or an infant born to a mother with systemic lupus erythematosus should be evaluated for manifestations of neonatal lupus including congenital heart block, hepatitis, and cytopenias. (2)

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the cutaneous manifestations of neonatal lupus erythematosus.

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Index of Suspicion in the Nursery

3 Neonate with Sudden Onset of Hypotonia on the Second Day After Birth

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AUTHOR DISCLOSURE Drs Sharma, Pandita, Murki, and Pratap have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-day-old 3-kg female term neonate is born in a normal vaginal delivery with Apgar scores of 8, 8, and 9 at 1, 5, and 10 minutes, respectively. During morning rounds, she is noted to have a weak cry. Antenatal and natal history findings are normal. Detailed neurologic examination shows a fully conscious neonate with decreased shoulder tone and head lag. Neonatal reflexes are also diminished, with a weak cry, poor swallowing, and poor sucking reflex. There are no clinical features of respiratory distress or respiratory failure, shock, seizure, or altered sensorium. The neonate is evaluated with a sepsis screen, serum glucose, serum calcium, serum electrolytes, and serum magnesium for neonatal sepsis or metabolic derangements. Laboratory investigation shows normal sepsis screen and metabolic evaluation (total white blood cell count of $13,000/\mu\text{L}$ [$13 \times 10^9/\text{L}$], C-reactive protein level of 0.01 mg/L [0.10 nmol/L], serum glucose of 89 mg/dL [4.9 mmol/L], total serum calcium of 8.4 mg/dL [2.1 mmol/L], ionized calcium of 4.6 mg/dL [1.1 mmol/L], serum magnesium of 1.3 mEq/L [0.65 mmol/L], serum sodium of 138 mEq/L [138 mmol/L], and serum potassium of 4.6 mEq/L [4.6 mmol/L]). Head neurosonography to rule out any bleeding or malformations has normal findings but neonatal hypotonia persists. At this time, one investigation clinches the diagnosis.

DISCUSSION

In a neonate with sudden onset of hypotonia, the initial differential diagnosis includes neonatal sepsis; metabolic derangements such as hypermagnesemia, hypocalcemia, and hypokalemia; antibiotic toxicity due to aminoglycosides; botulism; and cerebral malformations or bleeding. The neonate was evaluated for metabolic causes and neonatal sepsis, and the investigation showed normal sepsis screen and metabolic profile, thus ruling out these causes. The infant had no history of receiving antibiotics and she was exclusively breastfed, thus ruling out elevated levels of aminoglycosides or infantile botulism as a cause. Head ultrasonography findings were normal, which ruled out bleeding or malformations as the cause. On taking a detailed antenatal and natal history again, the mother was found to have myasthenia gravis (MG), for which she was taking pyridostigmine for the past 5 years and was asymptomatic. The infant was evaluated with anticholinergic receptor antibodies. The infant was started on tube feedings and was observed for respiratory distress or failure or worsening of hypotonia, with monitoring of vital parameters. The laboratory

results showed the presence of anticholinergic receptor antibodies with very high titers (8.8 mmol/L; normal range, 0–0.25 mmol/L), thus confirming a diagnosis of congenital MG.

Treatment

The neonate was started on oral pyridostigmine treatment (9 mg/kg per day) with continuation of tube feeding. She gradually showed improvement in muscle tone and on day 3 after starting treatment, she began breastfeeding. Her cry normalized and she was discharged on day 7 after birth. The infant was followed up regularly and treatment with pyridostigmine was stopped at age 4 weeks. The infant's muscle tone was appropriate for age at this time, and she received regular follow-up with no recurrence.

The Condition

MG is an autoimmune disease resulting secondary to the antibodies that are directed against the postsynaptic membrane of the neuromuscular junction. This leads to muscle weakness and easy fatigability of skeletal muscles.

Congenital MG is usually transient and results from transplacentally acquired antibodies of the mother. This condition is transient, therefore asymptomatic neonates require regular follow-up for early identification of hypotonia. If the neonate is symptomatic, as in the current case, then it is considered an indication for starting pharmacotherapy. The infant recovers as the effect of antibodies wanes.

Congenital myasthenic syndromes (CMS) include heterogeneous genetic diseases that are characterized by defective neuromuscular transmission. CMS can be classified as presynaptic, synaptic, or postsynaptic, depending on the primary defect's location within the neuromuscular junction. Difficulty in limb movement and associated hypotonia in a neonate are usually secondary to the neuromuscular junction disorder. Neuromuscular transmission is defective, finally leading to muscle exhaustion and decrease in tone. Most cases of CMS are transient and neonates gradually recover as the effects of antibodies wears off, but in a few cases, CMS is lifelong. Transient neonatal MG (TNMG) is usually seen in approximately 10% to 20% of neonates whose mothers are affected by MG. (1) Most of these mothers have clinically active manifestations of MG, but occasionally, the mother may be in the remission phase before the birth, thus making it difficult to suspect TNMG as in the current case. (2)

MG is classified as an autoimmune disorder in which acetylcholine receptor (AChR) antibodies are directed against the AChR of the neuromuscular junction. These

antibodies thus block the receptors of acetylcholine, and affect postsynaptic neuromuscular transmission. (3) Maternal AChRs are transferred in utero and these antibodies are responsible for the TNMG seen in these neonates. (1) (4) The recurrence risk of TNMG, if a previous neonate was affected, is up to 70% to 75% in the next pregnancy. TNMG is of 2 types, namely, seronegative MG and seropositive MG. In seronegative MG, the diagnosis is made only on clinical, electrophysiological, and pharmacological bases, and AChR antibodies are absent, whereas in seropositive MG, AChR antibodies are present in high titers, as in the current case.

Clinical Features

TNMG typically presents within the first few hours after birth (never reported after day 3 after birth) with definite signs being seen by the third day of postnatal age. (5) More severely affected infants have a history of polyhydramnios in utero and may present with arthrogryposis multiplexa at birth. Infants with TNMG have generalized weakness and hypotonia with typical presence of deep tendon reflexes. (4) Facial diplegia is seen commonly, and in contrast to MG seen in adults, ptosis and ophthalmoplegia occur less frequently. Bulbar weakness is frequent, leading to poor sucking, swallowing, and a weak cry. Pooling of secretions and respiratory muscle weakness may lead to respiratory failure requiring ventilatory support. (1)

Diagnosis

TNMG should be suspected in a neonate whose mother is diagnosed with MG. If the mother does not have MG, the diagnostic test result is the response of the infant to administration of an anticholinesterase inhibitor. The agent used most commonly is neostigmine methylsulfate (0.15 mg/kg intramuscular or subcutaneous). The result is considered positive when clinical improvement is noted in roughly 15 minutes and continues for 1 to 3 hours. Atropine may be needed to control muscarinic side effects such as diarrhea and increased tracheal secretions. This test should be conducted in a hospital setting where resuscitation facilities are available. Intraventricular hemorrhage or hypoxic-ischemic encephalopathy may occasionally interfere with an infant's response to the administration of an anticholinesterase inhibitor. In these conditions, repetitive nerve stimulation is provided to support the diagnosis. (6) This test compares the amplitude of the fifth evoked compound muscle action potential to the first, before and after administration of an anticholinesterase-inhibiting agent. A positive response is a reduction of the fifth action potential by 10% or more

and reversal of this decrement by the anticholinesterase inhibitor. (1)

Management

Management for neonatal myasthenia is mainly supportive. Small frequent feedings are provided by nasogastric or orogastric tube, and assistive ventilation is given if required. In addition, neostigmine methylsulfate (0.05 to 0.1 mg/kg intramuscular or subcutaneous) is given 30 minutes before each feeding. When feeding and respiratory abnormalities improve, neostigmine is given orally (0.5 to 1.0 mg/kg approximately 45 minutes before eating). Excessive doses may result in increased secretions, diarrhea, weakness, and muscle fasciculations. Pyridostigmine can also be used as an alternative drug. With continued clinical improvement, the dosage is decreased gradually. In addition, the course of the disease can be monitored with repeat nerve stimulation testing and measurement of AChR antibodies. Most patients (~90%) recover fully before age 2 months. Tube feeding and assisted ventilation are rarely required for more than 1 to 2 weeks, with the drug being required for an average duration of 4 weeks. (7)(8)(9)

Lessons for the Clinician

- Transient neonatal myasthenia gravis is an infrequently seen condition.
- All neonates born to mothers with myasthenia gravis need to be monitored closely for clinical manifestations of neonatal myasthenia gravis.
- Treatment is with the administration of anticholinesterase inhibitor and usually is needed for 4 to 6 weeks.
- Prognosis is excellent, with most neonates improving with no sequelae.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the basis for (including genetic) and clinical and laboratory features (including associated abnormalities), differential diagnosis, management, and outcomes of neonatal hypotonia/neuromuscular weakness.

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Parent Resources from the AAP at HealthyChildren.org

- Pulse Oximetry Screening to Detect Newborn Congenital Heart Disease <https://www.healthychildren.org/English/ages-stages/baby/Pages/Newborn-Pulse-Oximetry-Screening-to-Detect-Critical-Congenital-Heart-Disease.aspx>
- Depression During & After Pregnancy: You Are Not Alone <https://www.healthychildren.org/English/ages-stages/prenatal/delivery-beyond/Pages/Understanding-Motherhood-and-Mood-Baby-Blues-and-Beyond.aspx>
- Birthmarks & Hemangiomas <https://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Birthmark-Hemangiomas.aspx>
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Index of Suspicion in the Nursery

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Neurologic Effects on a Newborn Exposed to Marijuana in Pregnancy

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AUTHOR DISCLOSURE Drs Suneja, Prokhorov, and Thekumparampil have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An early term male neonate was born at 38 weeks of gestation by cesarean delivery due to a category 2 fetal heart tracing found in his 22-year-old mother, who did not receive prenatal care. Prenatal history is significant for maternal marijuana use, cigarette smoking, and group B *Streptococcus* colonization. At delivery, the infant is vigorous with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively, birthweight of 2,640 g, and no dysmorphic features noted on physical examination. Prenatal marijuana exposure is confirmed by maternal and infant urine toxicology results. In the first postnatal day, despite several attempts at feeding, a poor suck and feeding pattern are noted. The neonate is transferred to the NICU for feeding and further evaluation. In the NICU, the infant receives intravenous fluids for the first 3 days after birth along with ongoing trials at oral feedings. Sepsis is ruled out based on negative findings. Chromosomal analysis, microarray, and acyl carnitine profile are negative. Brain ultrasonography and magnetic resonance imaging, performed to rule out any hemorrhage or structural anomalies, are also negative. Gradually with oral stimulation therapy, the infant's sucking and oral coordination improved. Seventeen days after birth, he is feeding 75 to 80 mL every 4 hours and is discharged from the hospital. Meanwhile, the infant also has mild prolonged neonatal indirect hyperbilirubinemia related to glucose-6-phosphate dehydrogenase deficiency with maximum bilirubin of 15.5 mg/dL (265.05 μ mol/L). The result of New York State newborn screening test is negative and the infant passed the hearing screen. On follow-up health supervision visits, the infant is noted to be feeding and growing well.

DISCUSSION

Widespread legalization of marijuana use in the United States has occurred in tandem with a rising trend in marijuana use during pregnancy. Research studies are being conducted on the effect of marijuana alone and its concomitant use with other drugs or substances during pregnancy and lactation.

Marijuana is one of the most common illicit drugs used in pregnancy. (1) Delta 9 tetrahydrocannabinol, the major chemical compound found in marijuana, is highly lipophilic, readily crosses the placenta, and is found in human milk. Cannabinoid receptors are found in the brain and in the uterine decidua. (2) Maternal urine testing continues to remain the most popular method of

drug testing. Various studies have shown adverse outcomes with the use of marijuana in pregnancy including preterm delivery, low birthweight, and stillbirth. (2) Conflicting reviews have been reported regarding the relation between marijuana use during pregnancy and congenital anomalies in neonates. (3) Several animal and retrospective human studies have been conducted to analyze the effect of marijuana use during pregnancy on infant neurodevelopmental outcomes and intelligence. In one study comparing 26 infants who were exposed to marijuana in utero with nonexposed infants of demographically matched mothers, significantly different arousal, regulation, and excitability were noted on the NICU network neurobehavioral scale. (3) However, no specific long-term neurodevelopmental effects have been reported in neonates related to maternal use of marijuana during pregnancy.

Lessons for the Clinician

- Marijuana use during pregnancy is rising in the United States, but data on its effects on infants are inadequate.
- This case brings forth the need for more extensive research to study the immediate and long-term effects

on infants exposed to marijuana prenatally and through human milk.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects on the fetus and/or newborn infant of maternal substance abuse (eg, heroin, cocaine, cannabis, methamphetamines, and tobacco).

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Parent Resources from the AAP at HealthyChildren.org

- Edible Marijuana Dangers: How Parents Can Prevent Pot Poisoning: <https://www.healthychildren.org/English/ages-stages/teen/substance-abuse/Pages/Edible-Marijuana-Dangers.aspx>
- Legalizing Marijuana Not Good for Kids: AAP Policy Explained: <https://www.healthychildren.org/English/ages-stages/teen/substance-abuse/Pages/legalizing-marijuana.aspx>

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

Case 1: Neurologic Effects on a Newborn Exposed to Marijuana in Pregnancy

Upma Suneja, Sergey Prokhorov and Rani Thekumparampil

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Index of Suspicion in the Nursery

2 Newborn with Acute-Onset Central Cyanosis

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PRESENTATION

AUTHOR DISCLOSURE Drs Gosavi, Murki, and Kiran have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A female infant of 31 weeks' gestational age and birthweight of 1.19 kg is born to a gravida 2 woman. The mother had received a complete course of antenatal steroids 2 days before delivery. There is no history of early infantile deaths, early-onset stroke, or coronary heart disease in any of the family members.

The infant is delivered via cesarean section for fetal bradycardia and maternal eclampsia. At birth, she requires resuscitation with bag and mask for 1 minute, which is followed by delivery room continuous positive airway pressure (CPAP). Respiratory distress in the immediate neonatal period is supported with bubble CPAP in the first 48 hours after birth. For hemodynamically significant patent ductus arteriosus (PDA), the newborn is treated with diuretics, inotropes, and then ibuprofen syrup from day 3 to day 6 after birth. Echocardiography performed on day 6 after birth shows a closed PDA and no structural heart defect or vegetation. On day 8 after birth, in view of recurrent apneas, positive sepsis screen, and a positive blood culture for coagulase-negative *Staphylococcus*, the infant is given intravenous vancomycin. Her general condition is improving; she is tolerating feeds and is being transferred to a stepdown unit.

On day 14 after birth, the infant develops repeated desaturations, which progress to recurrent apnea over the duration of 12 hours. She continues to require an increasing fraction of inspired oxygen (FiO₂), bubble CPAP, and then ventilation with 100% FiO₂. On examination, the infant has central cyanosis, lethargy with decreased spontaneous activity, normal capillary refill time, and well-palpable pulses. Noninvasive blood pressure is 62/37 mm Hg with a mean arterial pressure of 45 mm Hg. The infant's urine output is 1.5 mL/kg per day and there is no evidence of abnormal weight gain, murmur, or abnormal heart sounds. The heart rate is consistently in the normal range. Even when receiving mechanical ventilation with 100% FiO₂, the newborn has central cyanosis with saturation in the range of 78% to 80%. Oxygen saturations in all 4 limbs are similar. The respiratory system is normal, with normal breath sounds and equal air entry on both sides. The infant shows no evidence of abnormal body movements or seizure activity.

The infant has a blood glucose measurement of 85 mg/dL (4.7 mmol/L); serum electrolyte measurements show a sodium level of 135 mEq/L (135 mmol/L), potassium of 3.9 mEq/L (3.9 mmol/L), and chloride of 103 mEq/L (103 mmol/L). On complete blood cell count evaluation, the infant has a hemoglobin level of 15 g/dL (150 g/L), packed red blood cell volume of 44.5%, total white blood cell count of 24,000/μL (24×10⁹/L) with 60% neutrophils, and platelet count of 65×10³/μL (65×10⁹/L). Coagulation profile shows a prothrombin time of 14.1 seconds, activated partial thromboplastin time of 44.8 seconds, fibrinogen level of

289 mg/dL (3.89 g/L), and C-reactive protein of 4.2 mg/L (40 nmol/L). Arterial blood gas shows a pH of 7.31, P_{aO_2} of 44 mm Hg (5.8 kPa), P_{CO_2} of 38.5 mm Hg (5.1 kPa), and base excess of -6.5. There is no evidence of methemoglobinemia; neurosonography findings are normal. Another investigation conducted at this point reveals the diagnosis.

DISCUSSION

Echocardiography showed large right atrial thrombus obstructing tricuspid flow intermittently with right to left flow through a patent foramen ovale (PFO) (Fig 1). Severe desaturations with normal pulse and normal blood pressures suggested a right to left flow through the PFO. Absence of difference in saturations between right upper and lower limb also suggested a shunt across the PFO. Negative sepsis screen with normal chest radiograph ruled out pneumonia. Low P_{aO_2} with low oxygen saturation and normal methemoglobin levels ruled out methemoglobinemia. There was no evidence of pulmonary hemorrhage clinically or on chest radiography.

The presence of umbilical line and coagulase-negative staphylococci sepsis may have contributed to the genesis of right atrial thrombus in this newborn. Absence of thrombus with a normal echocardiogram on day 6 after birth when documenting PDA closure suggested that the onset of thrombus was after that day. Progressive increase in size

with consumption of platelets resulted in repeated desaturation, apneas, and thrombocytopenia. Lethargy and hypotonia were due to hypoxia.

MANAGEMENT

The newborn was treated with mechanical ventilation, fluid bolus, and inotropic support. A percutaneous intravenous central line was introduced in the right upper limb, ensuring that the tip was placed in the right atrium. The tip position was confirmed with chest radiography. Thrombolysis was attempted with recombinant tissue plasminogen activator at 0.1 mg/kg per hour for 6 hours. The infant also received platelet and fresh frozen plasma transfusion during this time. After 6 hours of thrombolysis, echocardiography showed significant reduction in the size of the atrial thrombus and a clinical improvement in saturations. Unfractionated heparin was started at 15 U/kg per hour, continued for the next 24 hours, and switched to subcutaneous low-molecular-weight heparin. Repeated echocardiography showed dramatic reduction in the size of the thrombus (Fig 2). The infant underwent extubation after 48 hours and was breathing room air by the next 48 hours. Intravenous vancomycin was continued for 10 days. Repeat blood culture for bacteria and fungi were sterile, and urine culture for fungus was also negative. The neonate received maintenance low-molecular-weight heparin until resolution of atrial thrombus and for 2 weeks.



Figure 1. Large right atrial thrombus obstructing the tricuspid valve (arrow).

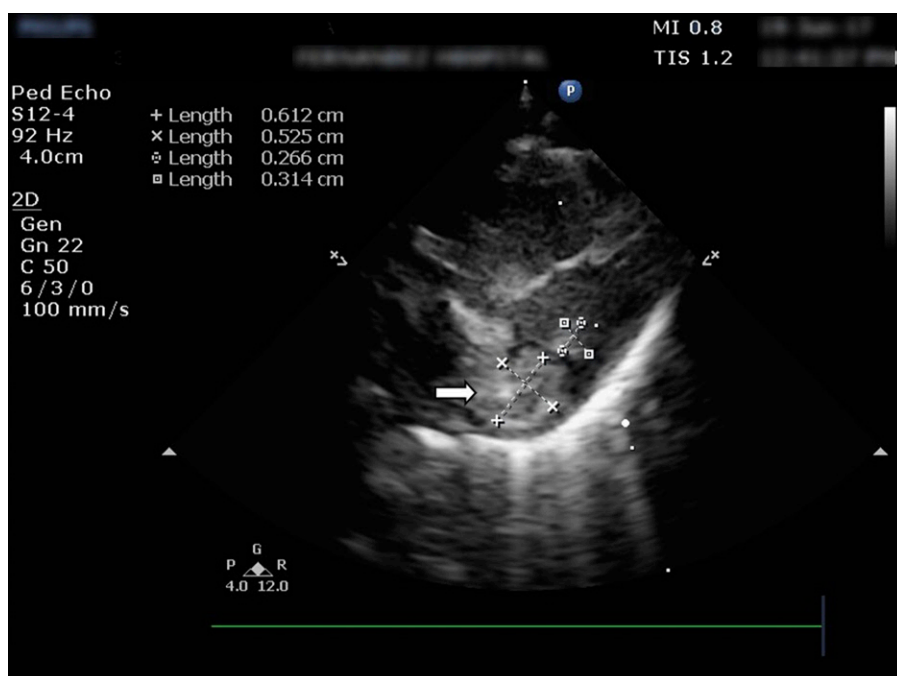


Figure 2. Atrial thrombus after 5 days of treatment (arrow).

NEONATAL THROMBOEMBOLISM

The incidence of neonatal thromboembolism is 6.8 per 1,000 NICU admissions. (1) The incidence remains the same in term versus preterm neonates as well as in male versus female neonates. (1) The neonatal coagulation system differs from those of children and adults, with a higher level of factor VIII and von Willebrand factor activity and low levels of factors II, VII, IX, X, XI, and XII. (2) These differences place the neonate in a relative prothrombotic state. Umbilical venous catheters and peripheral central venous catheters are commonly used in neonates. One study found that 21.4% of 28 infants with umbilical venous catheters had thrombus formation. (3) In neonates, intracardiac thrombosis is a rare event, with the incidence reported to be between 0.7 and 2.4 per 1,000 admissions; almost 90% of these are related to the use of central venous catheters. Intravascular catheters act as a nidus for platelet and fibrin accumulation and can damage the endothelium. (4)(5) Intracardiac (mainly right atrial thrombi) thrombosis is life-threatening because of the risk for dissemination of emboli into the lungs, obstruction of the right pulmonary artery, and obstruction of the tricuspid valve producing a pure right to left shunt across the PFO. (6)(7)

Lessons for the Clinician

- Intracardiac thrombosis is a life-threatening complication.

- Acute/subacute onset severe cyanosis, no lung findings, and absence of differential cyanosis should point to a right to left shunt across a patent foramen ovale.
- Thrombolytic therapy, mainly recombinant tissue plasminogen activator, for use in neonates, should be reserved for limb, organ, and/or life-threatening thromboses, including right atrial thromboses.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the causes and clinical manifestations of catheter complications of parenteral nutrition.
- Know the causes and pathophysiology of neonatal thrombocytopenia and thrombocytosis.
- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.

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Case 2: Newborn with Acute-Onset Central Cyanosis

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Case 2: Newborn with Acute-Onset Central Cyanosis

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Index of Suspicion in the Nursery

3 Newborn with Asymmetric Crying Face

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AUTHOR DISCLOSURE Drs Amphaiphan, Tim-Aroon, and Ruangkit, have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 35-week-gestation male infant is delivered by cesarean section in the setting of maternal premature rupture of membrane and fetal nonreassuring heart tracing during the process of labor induction. The mother is a 30-year-old, gravida 2, para 1, healthy woman without significant medical history. Maternal antenatal testing results are normal with unremarkable prenatal complications. The neonate is the product of a nonconsanguineous marriage. At birth, the infant's head is delivered without instrumental assistance or birth trauma. He is vigorous and cries immediately after birth. Resuscitation efforts include a brief period of continuous positive airway pressure and oxygen support for increased work of breathing and desaturation; however, the infant recovers quickly and is transferred to the sick newborn unit in room air. His Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. Physical examination reveals a nondistressed premature infant with normal vital parameters. His birthweight, length, and occipitofrontal circumference are 1,840 g, 39 cm, and 31.5 cm, respectively. He is found to have an asymmetric crying face. When he is quiet or sleeping, his face appears symmetric. However, when he cries, the left corner of the mouth is drawn to the left and downward while the right corner does not move. The forehead wrinkling, nasolabial fold depth, and eye closure remain intact and equal on both sides (Fig 1). All extraocular muscle movements are intact. He has an overfolded helix with squared superior portion of helix of bilateral ears and micro-retrognathia (Fig 2). Other physical examination findings are unremarkable. There is no history of a similar condition on both sides of the family.

DISCUSSION

Diagnosis

On day 3 after birth, systolic ejection heart murmur grade 3/6 is heard mostly at the left upper parasternal border on routine daily physical examination. Chest radiography demonstrates normal lung parenchyma and globular-shaped heart with absence of a thymic shadow. Echocardiography reveals a 2.2-mm ostium secundum atrial septal defect with left-to-right shunt, 4-mm subpulmonic ventricular septal defect with left-to-right shunt, and double outlet of right ventricle. Cranial and renal ultrasonography findings are normal. Chromosome study reveals 46,XY. Fluorescent in situ hybridization for 22q11 shows deletion. The neonate is diagnosed with congenital hypoplasia of depressor angularis oris muscle (CHDAOM) on the right side and 22q11.2 deletion syndrome. Further laboratory investigation



Figure 1. When the infant is at rest, the face appears symmetrical (left). When the infant is crying, the left corner of the mouth is drawn to the left and downward (right).

during hospitalization reveals a normal complete blood cell count, electrolytes, calcium, phosphate, and parathyroid hormone levels.

Condition

Asymmetric crying facies (ACF) is a condition in which an infant's face appears symmetric at rest and asymmetric when crying, that is, 1 corner of the mouth is pulled downward while another corner is not moving. (1) ACF can result from facial nerve compression to mandibular branch of facial nerve during the process of labor, leading to nerve injury. Another

cause of ACF is hypoplasia or agenesis of the muscles that involve downward movement of lips, namely, depressor angularis oris muscle and depressor labii inferioris muscle, the latter being less common. ACF is a minor anomaly occurring in 3 to 8 per 1,000 live births and predominantly affects the left side more than the right side. (2) This condition needs to be differentiated from facial nerve paralysis, which can be congenital (due to genetic defects) or, more commonly, acquired (from obstetric-related nerve trauma). In ACF, facial asymmetry presents as 1-sided downward movement of the mouth and symmetric eye closure, whereas in true facial nerve paralysis, all the facial muscles on 1 side are affected.



Figure 2. Infant facial features from right and left lateral views, showing overfolded helix with squared superior portion of helix of bilateral ears and microretrognathia.

The ACF that results from CHDAOM can be differentiated from the ACF caused by trauma using several approaches. First, based on the patient history, if obstetric risk factors for fetal compression are present (eg, large fetus, difficult labor, instrumental delivery), nerve compression can be suspected. Second, mandibular asymmetry and maxillary-mandibular asynclitism (nonparallelism of the gums) found during physical examination are important clues to the diagnosis of ACF resulting from nerve branch injury. Finally, further investigation using ultrasonography of facial muscles to ensure the absence or hypoplasia of depressor angularis oris muscle and electrodiagnostic testing to ensure paucity of motor unit potentials, lack of muscle fibrillation, and normal conduction velocity of the facial nerves may be useful to confirm a diagnosis of CHDAOM. (3)

The cause of the CHDAOM is not known; however, the pattern of inheritance does not suggest a single gene disorder, but favors complex multiple causative factors. (4)(5) Many other congenital anomalies may be present in infants with ACF that results from developmental error in muscle or nerve development. (6) The risk of associated anomalies in infants with ACF is 3.5-fold higher than in normal infants and it is reported that 5% to 70% of infants with ACF have associated anomalies, depending on the population and study criteria. (2) The common associated anomalies occur in the head and neck (48%), cardiovascular system (44%), musculoskeletal (22%), genitourinary tract (24%), central nervous system (10%), gastrointestinal tract (6%), and miscellaneous minor anomalies (8%). (4) Common head and neck anomalies are auricular malformation (dysplastic or hypoplastic ears, low-set ears, preauricular tags), mandibular or maxillary hypoplasia and palate anomaly. Common cardiac anomalies are atrial septal defect, ventricular septal defect, and patent ductus arteriosus. Other types of congenital heart diseases have also been reported. In other organ systems, various associated anomalies include those of the musculoskeletal system (syndactyly, clinodactyly, cortical thumb, hemivertebra), genitourinary system (inguinal hernia, renal hypoplasia, vesicoureteral reflux, cryptorchidism), central nervous system (auditory dysfunction, agenesis of the corpus callosum, hydrocephalus, brain cyst), and gastrointestinal system (esophageal atresia, imperforate anus, megacolon). (2)(4)(7)

The association of ACF and 22q11 deletion syndrome is well-described. Pasick et al report a 14% incidence of ACF in patients with a 22q11 deletion syndrome, which is significantly higher than in the general population. (6) In addition, various genetic syndromes, including trisomy 21, 4p deletion, Klinefelter syndrome, and VATER association (vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia), are diagnosed in patients with ACF. (2)(5)(7)

Treatment

In the case of nerve compression, the prognosis is good and spontaneous resolution is expected. In contrast, in the case of CHDAOM, spontaneous resolution is less likely. (2) However, treatment of CHDAOM is usually not required because the asymmetry will become less obvious as other facial muscles compensate for the child's facial expression when the child grows up. In those who need treatment for cosmetic purposes or to correct functional deficit and improve quality of life, various therapeutic strategies are available. These include plastic-reconstructive procedures on the lower lip on the affected side or additional blocking/weakening of the contralateral nonaffected side. (8) Associated congenital malformation and genetic syndromes are managed accordingly.

Progression

The infant described here developed clinical congestive heart failure at 1 week of age. Treatment consisted of fluid restriction, diuretics (furosemide and spironolactone), and digitalis glycosides (digoxin), and resulted in significant clinical improvement. The patient passed the otoacoustic emissions hearing screening and was discharged from the hospital in stable condition at the age of 2 weeks. The parents were counseled about the prognosis of CHDAOM and 22q11.2 deletion syndrome. Parental genetic tests to detect chromosome 22q11 deletion were recommended to provide guidance for future pregnancies.

Lessons for the Clinician

- Asymmetric crying facies (ACF) is not uncommon and can be found in approximately 3 to 8 per 1,000 live births.
- Physicians should be able to differentiate between ACF and true facial nerve paralysis.
- Congenital hypoplasia of depressor angularis oris muscle can be associated with other congenital malformations and genetic syndrome. Therefore, a thorough physical examination and diagnostic evaluation are required.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the significance of persistent neuromotor abnormalities in infancy (including asymmetries).
- Know the clinical and diagnostic features of the DiGeorge sequence (velocardiofacial syndrome, 22q11 deletion).

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Parent Resources from the AAP at HealthyChildren.org

- Micrognathia & Pierre Robin Sequence: <https://www.healthychildren.org/English/health-issues/conditions/Cleft-Craniofacial/Pages/Micrognathia-Pierre-Robin-Sequence.aspx>
 - Infantile Spasms: What Parents Need to Know: <https://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Infantile-Spasms-What-Parents-Need-to-Know.aspx>
 - Children with Facial Asymmetry: <https://www.healthychildren.org/English/health-issues/conditions/Cleft-Craniofacial/Pages/Children-with-Facial-Asymmetry.aspx>
 - Umbilical Cord Care: <https://www.healthychildren.org/English/ages-stages/baby/bathing-skin-care/Pages/Umbilical-Cord-Care.aspx>
- For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

Case 3: Newborn with Asymmetric Crying Face
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Case 3: Newborn with Asymmetric Crying Face

Kiengkwan Amphaiphan, Thipwimol Tim-Aroon and Chayatat Ruangkit

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Index of Suspicion in the Nursery

2 Newborn with Persistent Apnea

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AUTHOR DISCLOSURE Dr Saarela has disclosed no financial relationships relevant to this article. Dr Kim disclosed she is a consultant for EMD Serono. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female neonate is born via spontaneous vaginal delivery to a 19-year-old primiparous woman at 35 1/7 weeks of gestation at a rural hospital following an uncomplicated pregnancy. The neonate initially cries at delivery but soon becomes apneic and bradycardic. She is resuscitated with positive pressure ventilation, chest compressions, and a dose of epinephrine via emergent umbilical vein catheter. Her heart rate is subsequently stable in a normal range for age. During the resuscitation, endotracheal intubation is not successful so she receives ventilation via laryngeal mask airway. Her Apgar scores are 1, 1, 4, 5, and 7 at 1, 5, 10, 15, and 20 minutes, respectively. Her physical examination findings immediately after resuscitation are pertinent for diffuse hypotonia and decreased responsiveness. Her blood gas shows a severe mixed acidosis with pH 6.7, partial pressure of carbon dioxide 68 mm Hg (9 kPa), and base deficit 27.

She undergoes intubation and passive cooling, and is transferred to the nearest NICU. She has moderate-to-severe encephalopathy on admission and undergoes therapeutic hypothermia for 72 hours. Her neurologic findings steadily improve, but she continues to be dependent on mechanical ventilation for prolonged periods of apnea.

DISCUSSION

Progression and Diagnosis

Brain magnetic resonance imaging at 5 days shows a few scattered punctate foci of ischemia in parenchymal white matter. Electroencephalography shows no seizures and excessive discontinuity, which improves in time. At 6 days, she fails extubation attempts due to recurrent apnea. At 13 days, she undergoes extubation but requires nasal noninvasive positive pressure ventilation due to prolonged episodes of apnea. A trial of caffeine is ineffective. The neonatology and child neurology teams continue to reassess and decide to test for congenital central hypoventilation syndrome (CCHS) given her persistent apnea without clear etiology or other neurologic signs or symptoms. Her CCHS testing is positive, with 27 alanine repeats on 1 allele of the *PHOX2B* gene.

She is evaluated for conditions associated with CCHS and has normal results on suction rectal biopsy, echocardiography, and 72-hour telemetry monitoring. She does not exhibit autonomic dysfunction. She receives a tracheostomy and begins to learn oral feeding skills.

The Condition

CCHS is caused by a mutation in *PHOX2B*, a gene important to the function of neural crest cells. (1) Clinically, this neurocristopathy is characterized by alveolar

hypoventilation and autonomic dysfunction. Normally, exon 3 of the *PHOX2B* gene contains 20 alanine repeats. In CCHS, in-frame duplications cause expansion to 24 to 33 alanine repeats. These polyalanine repeat mutations (PARMs) are responsible for 92% of CCHS cases with a correlation between the number of repeats and severity of symptoms. In 8% of cases, the patient has a non-PARM in *PHOX2B*, such as a missense, nonsense, or frameshift mutation. (1) Most CCHS cases occur de novo, though some are inherited from a parent with somatic or germline mosaicism. A mutation in 1 *PHOX2B* allele is sufficient to cause CCHS (autosomal dominant). (1)

Although alveolar hypoventilation is the hallmark of CCHS, the role of *PHOX2B* in other neural crest-derived tissues predisposes affected individuals to a number of other conditions (2):

1. Gastrointestinal
 - a. Hirschsprung disease
 - b. Esophageal dysmotility
 - c. Intestinal dysmotility
 - d. Severe constipation
2. Cardiovascular
 - a. Bradycardia
 - b. Sinus pauses
 - c. Decreased heart rate variability
 - d. Attenuated heart rate response to exercise
3. Ophthalmologic
 - a. Pupillary abnormalities
 - b. Altered accommodation
4. Psychologic
 - a. Decreased perception of anxiety
5. Respiratory
 - a. Alveolar hypoventilation
 - b. Lack of arousal response to hypercarbia and hypoxemia
6. Pseudomotor
 - a. Sporadic, profuse sweating
 - b. Decreased basal body temperature
7. Oncologic
 - a. Neuroblastoma, related tumors

Natural History. CCHS is usually diagnosed in the newborn with cyanosis or disordered breathing. However, less severe cases may not be diagnosed until childhood or even adulthood. (2) Life expectancy for patients with CCHS can be normal depending on the timing of diagnosis, neurologic sequelae, severity of the phenotype, and adequate delivery of ventilator support. Respiratory failure is the most common cause of death. In addition, individuals with prolonged respiratory rate intervals without a pacemaker are at risk for sudden death. This risk is positively correlated with the number of polyalanine repeats and respiratory rate interval duration. (3) Neural crest tumors (eg, neuroblastoma) occur in 5% to 6% of children with CCHS, a 500-fold increased incidence compared with the general population. (4)

Secondary complications of CCHS may be lessened by optimizing oxygenation and ventilation. (2) Neurocognitive impairment has long been noted in the CCHS population. Developmental delays in preschool-aged children with CCHS have recently been described. (5) The etiology of the delays is likely multifactorial, including repeated hypoxic and hypercapnic episodes as well as brain maldevelopment and grey matter changes inherent to CCHS. (6)(7)

Lessons for the Clinician

CCHS, while rare, is an increasingly recognized neurocristopathy. It is important for the clinician to keep a high index of suspicion for CCHS in patients with alveolar hypoventilation or respiratory depression. CCHS is diagnosed by *PHOX2B* sequencing. (2) Once diagnosed, providing ventilation and evaluating for associated conditions are vital to caring for the patient with CCHS. (1)

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the indications for and limitations of various neurodiagnostic tests.

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Case 2: Newborn with Persistent Apnea

Katelyn Saarela and Amanda J. Kim

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Index of Suspicion in the Nursery

2 Newborn with Seizures, Renal Failure, and Weight Loss

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AUTHOR DISCLOSURE Drs Spence, Hong, and Davis have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-day-old male infant born at 37 weeks' gestation to a gravida 1, para 1 mother is transferred to the PICU of an academic medical center for concerns of weight loss, electrolyte derangement, and seizure activity. Prenatal laboratory results are unremarkable, with the exception of *Chlamydia* infection that is treated in the first trimester and group B *Streptococcus* infection that is adequately treated during delivery. The infant's Apgar scores are 9 and 9 at 1 and 5 minutes, respectively. His birthweight is 2,722 g (3rd percentile), his length is 46 cm (3rd percentile), and his head circumference is 32 cm (3rd percentile). He receives formula in the newborn nursery and is noted to have frequent episodes of emesis, prompting a change in formula type before discharge. He has 1 meconium stool and several wet diapers. He is discharged 2 days after birth with a weight of 2,580 g (3rd percentile).

He is seen by his pediatrician 4 days after birth and now weighs 2,126 g, 22% lower than his birthweight. He again is noted to have frequent episodes of emesis. The pediatrician refers him for admission to a local hospital for failure to thrive. Admission laboratory findings include: glucose, 105 mg/dL (5.8 mmol/L); sodium, 148 mEq/L (148 mmol/L); potassium, 7.1 mEq/L (7.1 mmol/L); chloride, 70 mEq/L (70 mmol/L); bicarbonate, 41 mEq/L (41 mmol/L); blood urea nitrogen, 100 mg/dL (35.7 mmol/L); creatinine, 4 mg/dL (353.6 μ mol/L); calcium, 8.7 mg/dL (2.1 mmol/L); total protein, 8.5 g/dL (85 g/L); albumin, 5.3 g/dL (53 g/L); total bilirubin, 11.7 mg/dL (200.1 μ mol/L); conjugated bilirubin, 1.6 mg/dL (27.3 μ mol/L); aspartate aminotransferase, 40 U/L (0.67 μ kat/L); alanine transaminase, 10 U/L (0.17 μ kat/L); and alkaline phosphatase, 185 U/L (3.09 μ kat/L). His complete blood cell count reveals the following: white blood cells, 9,400/ μ L (9.4×10^9 /L); hemoglobin, 18.3 g/dL (183 g/L); hematocrit, 59.5 g/dL; platelets, clumped; neutrophils, 38%; lymphocytes, 47%; and monocytes, 15%. These laboratory results reveal hyperkalemia, renal failure, and metabolic alkalosis.

He receives a 20-mL/kg normal saline bolus, calcium gluconate 40 mg intravenously (IV), sodium polystyrene 8 g rectally, ampicillin 100 mg IV, and gentamicin 5 mg IV. Our facility is contacted to arrange transfer. When our critical care transport team arrives to assess the patient, he is having active seizures with leftward eye gaze and extension of his extremities. He receives phenobarbital 10 mg/kg as an IV load, resulting in seizure cessation, and he is transported to our PICU.

On admission, he appears ill, lethargic, and cachectic. Physical examination reveals overlapping cranial sutures, brisk pupillary response, dry mucous membranes, and a scaphoid abdomen with no palpable masses. He undergoes intubation for impending respiratory failure. Repeat laboratory studies confirm the electrolyte derangements with the following changes: potassium, 4.1 mEq/L

(4.1 mmol/L); blood urea nitrogen, 302.5 mg/dL (108 mmol/L); creatinine, 3.62 mg/dL (320.08 μ mol/L); calcium, 31.2 mg/dL (7.8 mmol/L); and phosphorous, 38.7 mg/dL (12.5 mmol/L). He receives 200 mg of calcium gluconate for symptomatic hypocalcemia. A head computed tomography scan is normal. A 7F 7-cm double-lumen vascular catheter is placed using ultrasound guidance in the right internal jugular vein for continuous venovenous hemofiltration (CVVH) for symptomatic hypocalcemia secondary to hyperphosphatemia. He receives ampicillin, ceftazidime, and acyclovir for suspected neonatal sepsis after a lumbar puncture is performed. Imaging is performed, which reveals the diagnosis.

DISCUSSION

Diagnosis

The patient receives CVVH for 30 hours and shows gradual improvement in his urine output and renal function. Renal ultrasonography reveals left-sided grade 1 hydronephrosis. His neonatal sepsis evaluation, including blood culture, catheterized urine culture, and lumbar puncture with herpes simplex virus polymerase chain reaction, is negative. An upper gastrointestinal series reveals a high-grade obstruction at the duodenum (Figs 1 and 2.) He is taken to the operating room where a diamond duodeno-duodenostomy for duodenal atresia is performed.

Serum creatinine reaches 0.64 mg/dL (56.5 μ mol/L) within 24 hours of starting CVVH and stabilizes at 0.4 to 0.5 mg/dL (35.3–44.2 μ mol/L) after renal replacement

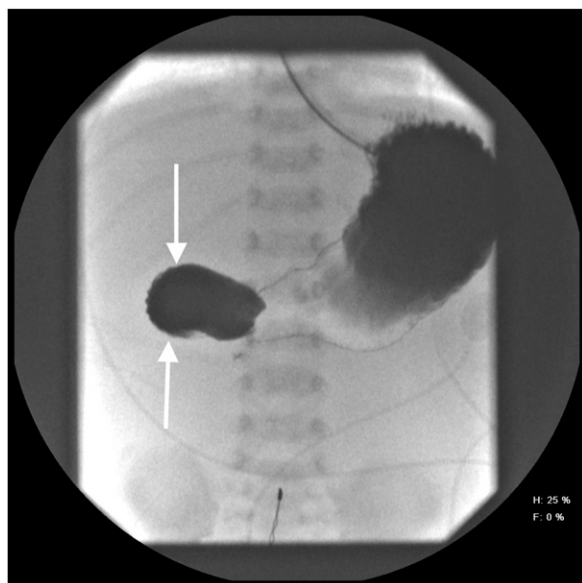


Figure 1. Upper gastrointestinal series showing dilated duodenal bulb (arrows) and absence of contrast distal to the duodenal bulb, consistent with duodenal atresia.

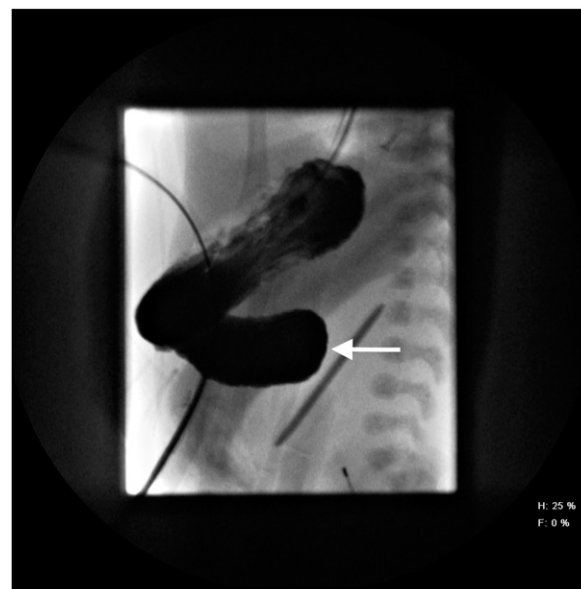


Figure 2. Upper gastrointestinal series lateral view showing dilated duodenal bulb (arrow) and absence of contrast in bowel distal to the duodenal bulb.

therapy is discontinued. He requires total parenteral nutrition for a prolonged period but is able to make a transition to full enteral feeds by 1 month after surgical repair. He is seen in clinic 2 months after his repair and is doing well clinically with weight-for-length now in the 85th percentile.

The Condition

The incidence of intestinal obstruction is estimated at 1 in 2,000 live births and is the most common newborn surgical emergency. The most common cause of neonatal intestinal obstruction is intestinal atresia, but it can also be caused by meconium ileus, Hirschsprung disease, and malrotation of gut with or without volvulus. Clinical presentation may vary from subtle findings, such as increased emesis, to cardiovascular collapse. Neonates with unrecognized intestinal obstruction experience rapid deterioration and require a high index of suspicion, thorough physical examination and timely radiographic studies. It is imperative to perform appropriate resuscitation and provide definitive treatment for optimal outcomes.

This patient presents with a striking metabolic alkalosis from loss of gastric secretions that are rich in chloride. Metabolic alkalosis is an acid-base disorder in which the pH of the blood is elevated above the normal range of 7.35 to 7.45. There are 5 major causes of metabolic alkalosis: gastrointestinal hydrogen losses, renal hydrogen losses, extracellular hydrogen losses, alkali administration, and contraction alkalosis.

Delayed recognition of this patient's high-grade intestinal obstruction likely caused prerenal acute kidney injury

that evolved into the intrinsic acute kidney injury on admission. His hyperkalemia corrected quickly and is indicative of total body potassium depletion secondary to gastric losses. His seizures were attributed to life-threatening hypocalcemia from hyperphosphatemia caused by his acute kidney injury.

Lessons for the Clinician

- Clinicians should have a high index of suspicion for bowel obstruction in a neonate who has frequent emesis, failure to thrive, and rapid deterioration in the newborn period.
- Metabolic alkalosis is indicative of gastrointestinal hydrogen losses, renal hydrogen losses, extracellular hydrogen losses, alkali administration, or contraction alkalosis. The presence of metabolic alkalosis may narrow the differential diagnosis.
- Electrolyte abnormalities can cause seizures in a neonate and prompt laboratory evaluation may guide management.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.

- Know the clinical manifestations of atresias, stenosis, diverticulae, and duplications of the small intestine including those associated with annular pancreas.

Suggested Readings

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Parent Resources from the AAP at HealthyChildren.org

- Seizures and Epilepsy in Children: <https://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Seizures-Convulsions-and-Epilepsy.aspx>
- Chronic Kidney Disease in Children: <https://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Chronic-Kidney-Disease-in-Children.aspx>

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

Case 2: Newborn with Seizures, Renal Failure, and Weight Loss

Tisha Spence, Jennifer Hong and Kasey Davis

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Index of Suspicion in the Nursery

1 Oral Burns as a Presentation of Accidental Organophosphorus Poisoning in a Neonate

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PRESENTATION

A 5-day-old girl is brought to the hospital emergency department for excessive crying. There is a history of accidental oral administration of a liquid insect repellent by her 3.5-year-old sibling ~2 hours earlier. The bottle brought by the parents reads “mosquito repellent.” Examination reveals an irritable, excessively crying baby, possibly due to pain. Her vital signs are essentially normal, with a temperature of 99.7°F (37.6°C), a heart rate of 146 beats/min, a respiratory rate of 52 breaths/min, a prompt capillary refill time, blood pressure of 90/56 mm Hg, and saturation of 100% in room air. Her pupils are of normal size and responding normally. Her oral cavity shows extensive burns involving the palate and posterior pharyngeal wall with bleaching of the mucosa (Fig). There are no dermal burns. Systemic examination findings are normal. Investigations show normal blood sugar levels and serum biochemistry results. Findings on chest radiography are normal. The active ingredient is confirmed by a forensic laboratory at All India Medical Institute of Medical Sciences, New Delhi, as dichlorvos (organophosphorus [OP] compound) with a pH of 3 to 5.

After admission, the baby's eyes are cleaned with distilled water and her body is sponged dry to eliminate further risk of absorption. The baby receives supportive treatment, is kept nil orally, and is administered intravenous fluids. Antibiotics are started, and the baby is monitored for cardiovascular instability. Orogastric feeds are started after 4 days of admission. The baby is monitored and watched to exclude systemic infections. Direct breastfeeding could be started by 2 weeks, when most of the oral lesions are healed. The baby is discharged and is doing well on follow-up at 3 months.

DISCUSSION

AUTHOR DISCLOSURE Drs Verma, Maria, and Singh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

OP compounds are commonly used as herbicides or insecticides in agriculture and households because they are relatively cheap and easily available. (1) Easy availability over the counter coupled with unsupervised use has led to an increase in the number of accidental and suicidal poisonings. Thus, neonates are rarely affected in such cases. Reported incidents among neonates have been



Figure. Extensive burns in the oral cavity of the patient caused by mosquito repellent.

the cases wherein the mode of exposure is transplacental, inhalation, or ingestion (accidental or homicidal). (2)(3)(4)(5)(6)(7)(8)(9) OP acts by inhibiting the enzyme cholinesterase in the central and peripheral nervous systems. The accumulated acetylcholine at synapses leads to cholinergic toxicity manifesting as miosis, bronchorrhea, excessive salivation, bradycardia, irregular respiration, and hyperpyrexia. (10) The local symptoms due to OP and features such as oral burns have not yet been reported to our knowledge. This case report presents an unusual case of oral burns in a neonate associated with accidental instillation of a domestic insecticide into the oral cavity by an older toddler sibling of the neonate.

Unlike in adults, where the poisoning is due to suicidal attempts, in infants it results from either unintentional accidental exposure or homicidal attempt. (2)(3)(4)(5)(6)(7)(8)(9) When affected, neonates are easily susceptible because of their large surface area. The signs and symptoms masquerade as neonatal sepsis. (5)(6)(7) Atropine being an antidote necessitates its differentiation for treatment. Typical muscarinic and nicotinic effects of OP poisoning are different in infants than in adults. Seizures, miosis, lacrimation, muscle weakness, dyspnea, and coma are common in infants. However, bradycardia, arrhythmia, hypotension, pulmonary edema, fasciculation, sweating, confusion, parkinsonism, psychosis, etc, are common in adults. (5)

Poisonings are difficult to identify in neonates because they require a high index of suspicion and exploration into preceding events as such incidents are not expected at this age. The diagnosis is based on history of exposure supported by the characteristic cholinergic signs. History of exposure may not always be evident. Presenting symptoms depend on dose, duration, route of

administration, and potency of the compound. The absorption of OP compounds could be through the gastrointestinal tract, skin, mucosal membranes (inhalational and through the conjunctiva), and, rarely, transplacental. The Table shows a brief review of the literature on cases of neonatal OP poisoning along with the management and outcome.

Oral burns are common manifestations of caustic and acid ingestion, caused by denaturation of surface proteins. The stronger the acid ($\text{pH} < 2$) or alkali ($\text{pH} > 11$), the higher its potency to cause burns. Acids cause extensive coagulative necrosis of proteins, whereas alkalies cause liquefactive necrosis of mucosa. Mucosal burns involving the oral cavity, esophagus, and stomach may culminate in stricture formation. The OP compounds rarely produce oral burns, and neonates may be more susceptible to the tissue-damaging effects of OP compounds because their mucosa is more fragile. However, it seems that this type of presentation probably reflects the milder end of the spectrum of presentation of OP poisoning. This infant had no systemic manifestations in the acute phase and recovered fully, with no sequelae on follow-up.

Unknown poisoning presenting with oral burns can be misdiagnosed if muscarinic or nicotinic symptoms are not present, as is the case with OP poisoning in neonates and children. In the presence of a specific antidote, a missed diagnosis can be fatal. The diagnostic hallmark of OP poisoning is reduction in serum and red blood cell cholinesterase activity. Although most cases of neonatal OP poisoning in the literature have been treated with atropine and pralidoxime (Table), we managed the case conservatively due to the absence of systemic symptoms. There was no dysphagia or feed intolerance in this infant. Because the infant was accepting feeds well and the lesions healed gradually, an endoscopy was deferred. In our case, with child abuse ruled out, the circumstantial evidence was overwhelming in favor of accidental OP poisoning, as confirmed by laboratory testing. The literature review does not have any record of a case of oral burns caused by OP compounds.

An OP compound poisoning warrants a differential diagnosis for the etiology of oral burns in neonates. Decisions should be made in the wake of clinical examination such that an absence of systemic toxicity should not be misleading.

Lessons for the Clinician

Little is reported about OP poisonings in neonates. This report may inform the treating physician with newer insights on this subject, especially the following:

- Neonatal age is not exempt from OP poisoning.

TABLE. Neonatal OP Poisoning: Literature Review

SOURCE	AGE, d	MODE OF POISONING	SIGNS AND SYMPTOMS	SERUM ACETYL CHOLINESTERASE LEVELS	TREATMENT GIVEN	OUTCOME
Sarkar et al, (2) 1994	1	Transplacental: propoxur	Copious secretions, miosis, flaccid paralysis, twitching	Not determined	Atropine, pralidoxime, supportive treatment	Death due to perinatal asphyxia and carbamate poisoning Duration of stay 4 d
Kaur et al, (3) 1996	25	Not known	Increased secretions, bradycardia, pinpoint pupils, hypotonia, irregular respiration	2.14 nmol product formed/min per mg protein	Atropine, pralidoxime, supportive treatment	Discharged healthy Duration of stay 20 d
Jajoo et al, (4) 2010	1	Transplacental: Diazinon	Shallow respiration, bradycardia, poor perfusion, profuse secretions, dilated pupils, twitching	Not determined	Atropine, pralidoxime, supportive treatment	Discharged healthy Duration of stay 12 d
O'Reilly and Heikens, (5) 2011	12	Compound not known: probable accidental topical exposure	Increased oral secretions, poor feeding, diarrhea, pinpoint pupils, hypotonia, pulmonary edema	Not determined	Atropine, supportive treatment	Discharged healthy Duration of stay 5 d
Parvez et al, (6) 2012	17	Diazinon spray: accidental topical absorption/ inhalation	Poor feeding, reduced activity, increased oral secretions, apnea, bradycardia, pinpoint pupils	137 U/L	Atropine, pralidoxime, supportive treatment, stopping breastfeeding	Discharged healthy on day 2, readmission, and again discharged
Chheda et al, (7) 2014	15	Homicidal ingestion: Thimet (10% phorate)	Excessive secretions from mouth, poor feeding, irregular respiration, nystagmus, pinpoint pupils	Initial: 466 U Repeated on day 2: 566 U	Atropine, pralidoxime, supportive treatment	Death due to multi-organ failure Duration of stay 4 d
Meena and Kumar, (8) 2014	6	Oral accidental exposure, compound not known	Poor oral acceptance, lethargic, jitteriness, increased nasopharyngeal secretions, hypotonia, pinpoint pupils	0.25 kU/L	Atropine, pralidoxime	Discharged healthy Duration of stay 6 d
Kumar et al, (9) 2015	8	Oral accidental ingestion of chlorpyrifos	Inconsolable cry, poor feeding, seizures, bradycardia, respiratory distress, pinpoint pupils, copious secretions	2,209 IU/L	Atropine, pralidoxime	Discharged healthy Duration of stay 18 d

- However, presentation may be unusual, such as oral burns.
- In the presence of circumstantial suggestion, OP poisoning must be considered, even if systemic cholinergic signs are absent.

ACKNOWLEDGMENT

We acknowledge Dr. A. Jaiswal, Scientist Poisoning Cell, All India Institute of Medical Sciences, New Delhi, for identifying the OP compound in our case.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the complications and management of various neonatal skin injuries, including intravenous infiltrates and chemical and thermal burns.

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Case 1: Oral Burns as a Presentation of Accidental Organophosphorus Poisoning in a Neonate

Ankit Verma, Arti Maria and Archana Singh

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1

Periorbital Swelling and Conjunctivitis in a Preterm Infant

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AUTHOR DISCLOSURE Drs Newman, Horan, and Kurtom have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A preterm male infant is born at 34 weeks of gestation to a 30-year-old gravida 1, para 0 woman with no significant medical history and good prenatal care. The family medical history is not significant. Prenatal serologic tests for syphilis, human immunodeficiency virus, and hepatitis B are negative and rubella status is immune. She develops gestational hypertension for which she undergoes antepartum observation for 3 weeks. After her condition progresses to preeclampsia with severe features, the decision is made to induce delivery. She receives antenatal corticosteroids and magnesium sulfate before delivery, as well as 5 doses of ampicillin for unknown group B *Streptococcus* status. The infant had been depressed at birth, with postresuscitation Apgar scores of 1, 5, and 8 at 1, 5, and 10 minutes, respectively. He is noted to have respiratory distress secondary to mild respiratory distress syndrome, is given noninvasive positive pressure ventilation, and begins empiric treatment with ampicillin and gentamicin after a blood culture specimen is collected. Initial laboratory findings, including complete blood cell count and electrolytes, are unremarkable. After 2 days, he makes a transition to a simple nasal cannula with room air, and oral feeds are started. Antibiotics are stopped after 2 days because blood cultures show no growth. After 4 days, he is noted to have temperature instability and apnea. Because of a concern for sepsis, blood and cerebrospinal fluid culture specimens are drawn and he is restarted on ampicillin and gentamicin treatment. The following day, the blood culture shows gram-negative rods and cefepime is added to his treatment regimen. On the 6th day after birth, he is noted to have periorbital swelling and erythema of the left eye with purulent drainage, conjunctivitis, and grey discoloration of the cornea. Ophthalmology consultation finds a large corneal infiltrate and corneal swelling (Fig). Two-dimensional (2D) mode ultrasonography is performed, which demonstrates diffuse vitreous haze along with a large retinal attachment. Culture specimen of the vitreous humor obtained during surgery confirms the diagnosis.

DIAGNOSIS

The differential diagnosis for a red, swollen eye in a newborn is broad. However, the combination of sepsis, clinical or culture proven, and noted hypopyon are suspicious for endophthalmitis. Given the lack of visibility of the anterior and posterior chambers on examination, 2D ultrasonography is indicated to evaluate the extent of infection. Magnetic resonance imaging was subsequently obtained,

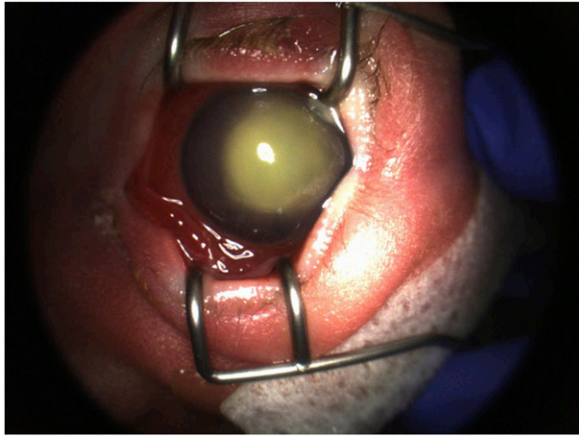


Figure. A large corneal infiltrate is seen, which appears to be of full thickness and encompasses approximately 60% to 70% of the corneal surface area. Surrounding corneal edema can be seen. The pupil and lens are not visible.

which showed diffuse enlargement of the globe, posterior displacement of the lens, and retrobulbar soft tissue enhancement. Given the risk of globe rupture and sympathetic ophthalmia, the decision was made to perform evisceration with subsequent placement of an acrylic implant. Specimens of the initial blood culture as well as of the vitreous taken after surgery were positive for *Serratia marcescens*, confirming the diagnosis of endogenous endophthalmitis. He received cefepime for a total of 21 days. The right eye was treated prophylactically with tobramycin ophthalmic solution. The infant was discharged 1 week later.

DISCUSSION

Neonatal endogenous endophthalmitis is a rare, potentially devastating infection of the inner eye, caused by hematogenous spread of pathogenic microorganisms. In the United States, its incidence has been decreasing at a rate of 6% per year. In 2006, 4.42 cases per 100,000 live births were reported. (1) The most common cause of endophthalmitis in newborns is fungal, secondary to candidemia. Group B *Streptococcus*, *Pseudomonas*, and other gram-negative rods account for the majority of bacterial infections. Transmission can occur vertically at the time of delivery, as is likely in the current case, or from contaminated catheters or respiratory equipment. (2) *S marcescens*, a rare cause of neonatal endophthalmitis, is mentioned only 5 times in the literature. (3)(4)(5)(6)(7) Associated risk factors are generally those seen frequently in preterm infants, including those with birthweights less than 1,500 g, candidemia, systemic bacteremia, retinopathy of prematurity, blood transfusion, respiratory disorders,

and perinatal infections. (1) It is hypothesized that the persistence of the tunica vasculosa lentis makes preterm infants uniquely susceptible. (2)

Bacterial endophthalmitis frequently presents with lid edema, conjunctival injection, corneal edema, and exudates in the anterior chamber. (8)(9) Pink hypopyon is a rare physical examination finding that may be seen with *Serratia* endophthalmitis, because of bacterial production of the pigment prodigiosin. (5)(9) Loss of the red reflex itself can be an early sign of endophthalmitis, as can conjunctivitis. The presence of a red eye or lack of a red reflex in any patient with sepsis should prompt full ophthalmologic evaluation. It is therefore recommended to examine the conjunctiva and red reflex of any newborn with signs of sepsis. Any concerning findings should prompt an immediate ophthalmology consultation. Diagnosis is made clinically based on anterior chamber findings or vitreous opacities. (2) Culture specimens from both the aqueous and vitreous humor should be sent, in addition to blood cultures to determine sensitivity to antibiotics. Treatment includes broad-spectrum systemic and intravitreal antibiotics. Outcomes are poor, and infection may result in evisceration or enucleation.

Lessons for the Clinician

- Ophthalmologic examination should be performed in all newborns to evaluate the conjunctiva, iris, and red reflex.
- Loss of the red reflex in an infant with sepsis may be an early sign of endophthalmitis.
- Ophthalmology should be consulted early for any suspected ocular infection.
- All suspected cases should be treated with broad-spectrum antimicrobials initially.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes and clinical and laboratory features of acute neonatal infections of the eyes, including ophthalmia neonatorum.

ACKNOWLEDGMENT

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3 Premature Infant with Anemia and High-Output Cardiac Failure

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AUTHOR DISCLOSURE Drs Weiner, Talmon, Peniakov, and Felszer-Fisch have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female singleton is delivered at 30 6/7 weeks' gestational age via cesarean for preterm labor and breech presentation. The mother is a 37-year-old grand multipara in her 10th pregnancy. The pregnancy is notable for severe fetal anemia, high-output cardiac failure with normal cardiac anatomy, polyhydramnios, and a placental chorioangioma diagnosed at 26 weeks of gestation. Evaluation for congenital infections is negative. At 25 and 28 weeks' gestation, the fetus had received in utero red blood cell transfusions for severe fetal anemia.

At birth, the infant has respiratory depression requiring intubation and ventilation. Apgar scores are 7, 6, and 8 at 1, 5, and 10 minutes, respectively, and her birthweight is 1,416 g. The neonate is noted to have a protuberant abdomen with significant hepatosplenomegaly, diffuse subcutaneous edema, petechiae, and ecchymoses.

The infant requires significant ventilator support for the first few weeks after birth. Chest radiography shows no evidence of pleural or pericardial effusion. Echocardiography shows normal cardiac segmental anatomy with significant biventricular hypertrophy, though blood pressure is maintained. Significant anemia, thrombocytopenia, and coagulopathy are noted over the first days after birth, for which the newborn requires multiple blood products. Profound jaundice necessitates multiple double-volume exchange transfusions. Thrombocytopenia and coagulopathy gradually improve over the first week after birth. However, the infant develops significant cholestasis, reaching a peak direct bilirubin of 12.5 mg/dL (213.8 μ mol/L) at 2 weeks of age.

DISCUSSION

The unique constellation of findings in this case, anemia, thrombocytopenia, high-output failure, and cholestasis, presented a broad differential diagnosis. The differential included congenital heart disease and vascular malformations, infectious etiologies, metabolic and genetic disorders, and various renal, hepatic, gastrointestinal, and hematologic pathologies. Sepsis evaluation was performed on admission and cultures were sterile. Evaluation for congenital infections and metabolic/genetic disorders was unremarkable. The infant was diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which may have contributed to the jaundice, but was not the sole reason for the profound cholestasis.

Abdominal ultrasonography revealed hepatosplenomegaly with 3 vascular lesions in the liver. Abdominal computed tomography scan further supported

the diagnosis of hepatic hemangiomas (Fig 1A), with tapering of the abdominal aorta below the celiac trunk suggesting the presence of hepatic arteriovenous shunting (Fig 1B). The infant received treatment with phenobarbital and ursodiol for the cholestasis, without significant improvement. Significant ventricular hypertrophy with left ventricular outflow tract (LVOT) obstruction and restrictive cardiac physiology resulted in elevated left atrial pressure and pulmonary congestion. In an attempt to reduce the size of the liver hemangiomas and improve the hypertrophic cardiomyopathy, treatment with propranolol was started on day 6 and the dose was gradually increased as tolerated.

The infant's clinical condition subsequently improved and she was weaned from ventilator support. The hepatic hemangiomas decreased in size and the cholestasis resolved. Phenobarbital and ursodiol therapy were discontinued. Several weeks later, although the LVOT resolved, the biventricular hypertrophy improved only minimally. At 2 months of age, a cutaneous hemangioma was noted on the abdomen. No further cutaneous hemangiomas were identified over the remaining hospital course.

The infant was discharged from the hospital at 3 months of age with mild chronic lung disease and mild residual hypertrophic cardiomyopathy on low-flow nasal oxygen

and propranolol. At 12 months of age, she was receiving propranolol but was weaned from oxygen. She had mild developmental delay and slow growth but was otherwise healthy. Liver ultrasonography showed complete resolution of the hepatic hemangiomas.

Diagnosis

The diagnosis was infantile hepatic hemangioma (IHH).

Pathophysiology

The clinical presentation, imaging findings, later appearance of a cutaneous hemangioma, and clinical improvement in response to propranolol therapy are all highly characteristic of IHH.

Infantile hemangioma is the most common vascular tumor seen in early infancy. It is a benign proliferation of endothelial cells that undergo a phase of rapid growth followed by spontaneous involution. The reported incidence is approximately 5% of healthy infants, and these lesions are more common in premature infants. (1) The term *benign neonatal hemangiomatosis* has been used to describe infants with numerous cutaneous hemangiomas without extracutaneous involvement, whereas diffuse or disseminated neonatal hemangiomatosis describes infants with both cutaneous and visceral hemangiomas.

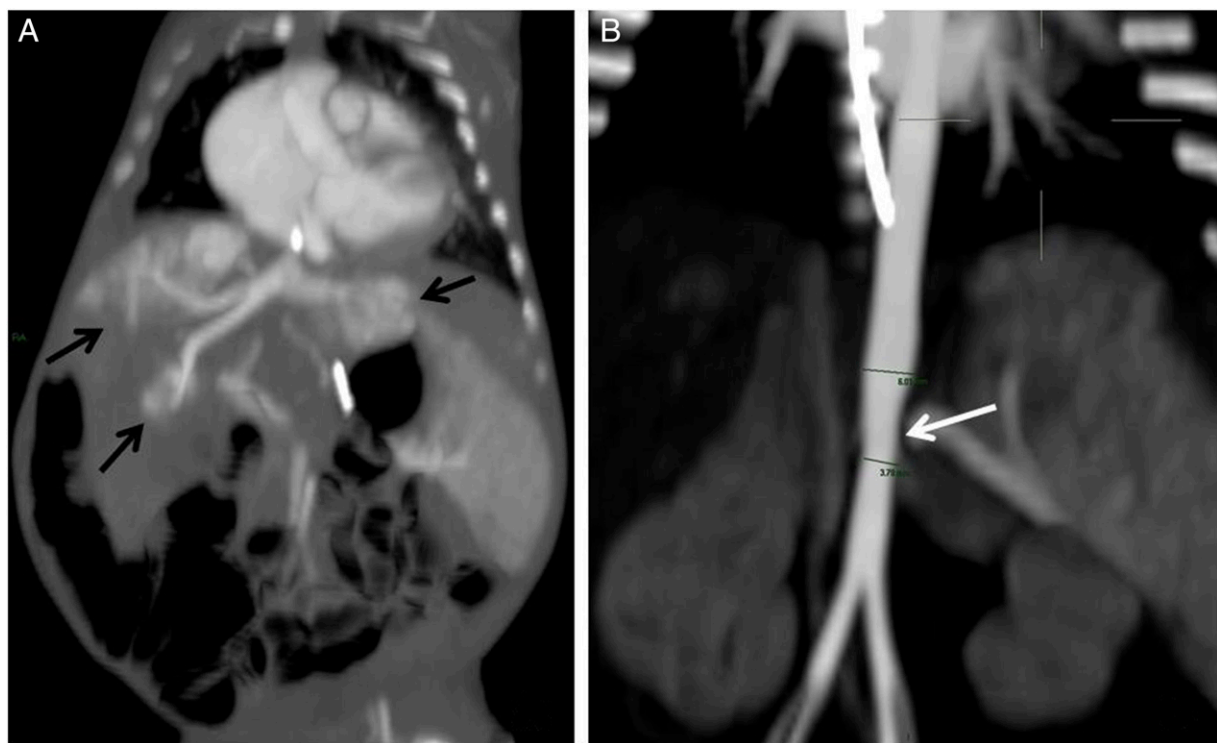


Figure 1. Computed tomography scan. A. Black arrows indicate locations of hepatic hemangiomas. B. White arrow demonstrates aortic tapering below celiac trunk.

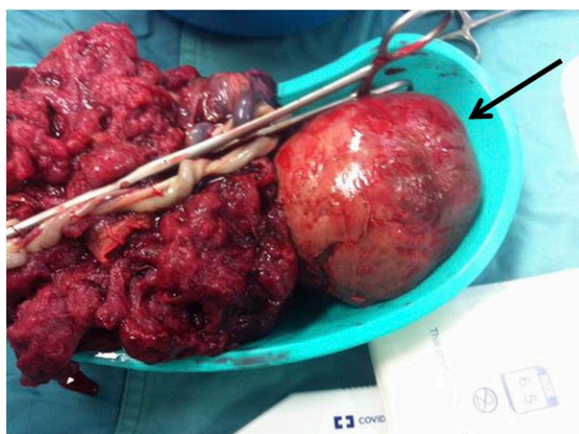


Figure 2. Placenta with chorioangioma. Black arrow indicates the chorioangioma, a firm, well-circumscribed mass measuring 10 cm in its greatest dimension, attached to the placenta.

(2) The latter has a significant mortality rate. The liver is the most common site for a visceral hemangioma, but the gastrointestinal tract, airway and lungs, central nervous system, and eyes may also be affected. Complications include high-output cardiac failure, visceral hemorrhage, and hypothyroidism.

Christison-Lagay et al proposed a subtype classification for IHH: focal, multifocal, and diffuse. (3) A review of this subtype classification approach suggested that focal lesions may represent a process biologically distinct from multifocal and diffuse disease, and most undergo spontaneous involution after birth. (4) This patient's lesion best meets the criteria of a multifocal hepatic hemangioma because the hepatic lesions continued to proliferate after birth and because of the presence of multiple hepatic lesions.

The initial course of the patient was complicated by severe hemolysis and profound cholestasis. It is likely that the rare combination of 3 pathologic hemolytic processes created the need for multiple exchange transfusions: a large placental chorioangioma, a multifocal hepatic hemangioma, and partial G6PD deficiency.

A unique aspect of the case was the finding of a placental chorioangioma measuring 8×8×10 cm (Fig 2). Placental chorioangioma is the most common benign tumor of the placenta, occurring in 1% of all examined placentas. Large tumors, those greater than 4 to 5 cm, are rare and associated with maternal and fetal complications, including polyhydramnios, fetal high-output cardiac failure and cardiomegaly, fetal hydrops, fetal anemia, and neonatal hemolytic anemia. Interestingly, multiple reports of neonatal hemangiomatosis occurring in association with large placental chorioangiomas can be found throughout the medical literature. (5) Both placental chorioangioma and infantile hemangioma are benign proliferations of capillary

endothelial cells, suggesting perhaps a common genetic mechanism or a shared trigger leading to a disturbance in embryonic mesodermal development in these patients. The “placental hypothesis” suggests that the pathogenic hemangioma precursor cell may derive from placental progenitor cells. (6)

The cardiac complications seen in this patient were likely the result of high-output cardiac failure related to the large placental chorioangioma, further compounded by the hepatic hemangioma. Despite the removal of the placental chorioangioma from the systemic circulation at birth, the cardiomyopathy, hemolysis, and liver dysfunction progressively worsened over the first weeks after birth, suggesting that the ongoing disease was secondary to the hepatic hemangioma. It could be argued that the rapid clinical improvement may have been the result of absence of the hemodynamic effects of the chorioangioma and/or the cessation of exposure to growth factors or mediators of angiogenesis possibly elaborated by the chorioangioma. Alternatively, it is possible that the hepatic lesion was “preprogrammed” to rapidly involute, as is typical, to a focal hepatic hemangioma. However, the timing of the clinical improvement, coinciding with the increased propranolol dosage and the subsequent shrinkage of the hepatic hemangiomas, argues that propranolol was the main driver of clinical improvement.

Management

Historically, systemic corticosteroid therapy has been the first-line agent for the treatment of IHH, with only limited success. Other agents (eg, interferon) have been no more effective and carry considerable risk of various concerning side effects. In addition, arterial embolization/ligation and surgical resection have been used as alternative treatment strategies. Over the past decade, propranolol has emerged as an effective treatment for severe infantile hemangiomas. (7) In the wake of this discovery, a growing body of clinical reports has described clinical response of IHH to propranolol. (8)(9) This patient similarly responded to propranolol without any side effects.

Lessons for the Clinician

- Infantile hepatic hemangioma may lead to high-output cardiac failure and may cause significant morbidity and mortality.
- Propranolol should be considered as a therapeutic option for infantile hepatic hemangioma.
- Large placental chorioangiomas have been found in association with hepatic hemangiomas and should prompt screening liver ultrasonography in the neonatal period.

ACKNOWLEDGMENTS

The authors wish to thank Drs Christison-Lagay, Etty Daniel-Spiegel, Amichai Rothstein, and Eric Shinwell for their assistance in preparing this article.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical and laboratory features and management of hemangiomas in the newborn.

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Case 3: Premature Infant with Anemia and High-Output Cardiac Failure

Scott A. Weiner, Gil Talmon, Marina Peniakov and Clari Felszer-Fisch

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Case 3: Premature Infant with Anemia and High-Output Cardiac Failure

Scott A. Weiner, Gil Talmon, Marina Peniakov and Clari Felszer-Fisch

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Index of Suspicion in the Nursery

1 Preterm Neonate with Hydrops and Lactic Acidosis

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PRESENTATION

A premature female infant is born to a 29-year-old woman with minimal prenatal care at 34 4/7 weeks of gestation, weighing 1,760 g. The woman had been diagnosed with human immunodeficiency virus (HIV) during her second trimester and treated with emtricitabine, tenofovir, and dolutegravir. The infant is delivered via urgent cesarean section because of ultrasound findings of reversed end-diastolic flow on Doppler with category III fetal heart tracings, growth restriction at the 5th percentile, pericardial effusion, and ascites (Fig). Intrapartum zidovudine prophylaxis is administered, but delivery occurred before 3 hours. Apgar scores are 1, 4, 6, and 7 at 1, 5, 10, and 15 minutes, respectively.

Physical examination demonstrates respiratory distress and generalized edema, notably over the extremities and abdominal wall. She undergoes intubation at delivery and initial laboratory tests show thrombocytopenia, elevated transaminases, and significant lactic acidosis (Table 1). Both the mother and infant have type B, Rhesus factor–positive blood.

Platelets are transfused, and nevirapine, lamivudine, zidovudine, and total parenteral nutrition are started. She receives ampicillin and gentamicin for 48 hours, with negative blood cultures. Abdominal ultrasonography on day 1 after birth identifies mild ascites, but no hepatomegaly or liver calcifications. Head ultrasonography finds no evidence of intracranial calcifications.

On day 2 after birth, she receives 1 dose of surfactant. Echocardiography is notable for mild right ventricular dysfunction and coronary vasculopathy with mild ectasia of both coronary arteries and a small pericardial effusion. She undergoes extubation 3 days after birth and respiratory support is weaned without further complications.

On day 5 after birth, fresh frozen plasma is transfused for an elevated prothrombin time (26.8 seconds) and international normalized ratio (2.4). Lamivudine and nevirapine are held, given hepatopathy, but zidovudine is continued for the HIV exposure, and ursodiol is started for significant direct hyperbilirubinemia. Ammonia levels are spuriously high (95 µg/dL [68 µmol/L]), likely from delayed laboratory analysis. Iron studies and ferritin are inconsistent with hemochromatosis.

Her generalized edema, liver enzymes, and bilirubin levels improve by the second week of age (Table 2) and ursodiol is discontinued 4 weeks after birth. Total parenteral nutrition is discontinued with advancement of her diet, complicated by hypoglycemia requiring slow weaning of dextrose intravenous fluids. Repeat echocardiography at 3 weeks of age shows improved coronary artery sizes with no evidence of ectasia or aneurysm.

NOTE The editors and staff of *NeoReviews* find themselves in the fortunate position of having too many submissions for the Index of Suspicion in the Nursery column. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will make an announcement in *NeoReviews* when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

AUTHOR DISCLOSURE Drs Szafron, Kazerouninia, and Gokulakrishnan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

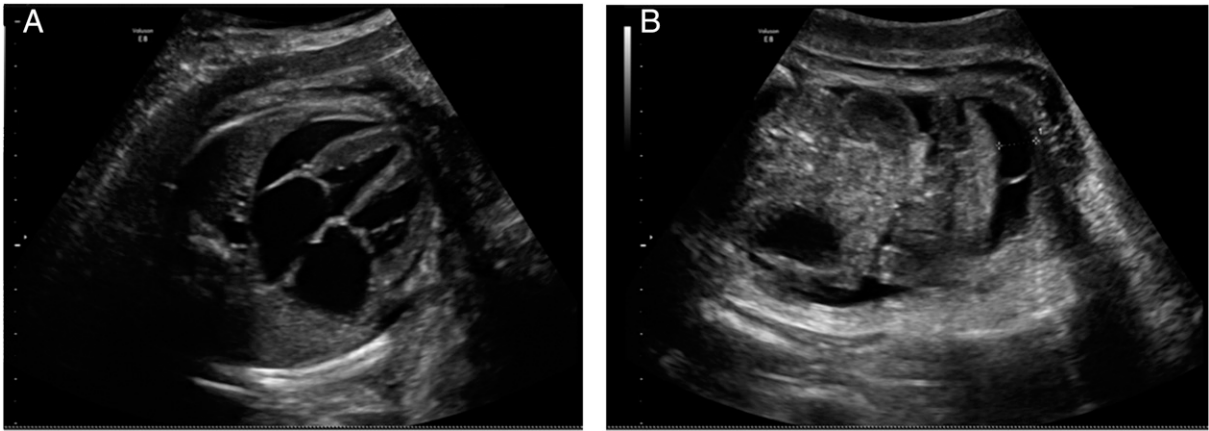


Figure. Pericardial effusion (A) and ascites (B) on fetal ultrasonography.

She is discharged at age 6 weeks and meets developmental milestones at the 2-month follow-up.

FURTHER TESTING

Maternal toxoplasmosis, other agents, rubella, cytomegalovirus (CMV), and herpes simplex (TORCH) studies are only positive for CMV viremia, but the patient's urine CMV polymerase chain reaction (PCR) is negative on 2 occasions.

HIV-1 RNA qualitative PCR is negative at birth, 2 weeks, and 6 weeks after birth. Serologies for HSV, parvovirus B19, syphilis, rubella, enterovirus, and toxoplasmosis are negative.

High-resolution cytogenetic analysis and state newborn screening results are normal. Brain MRI shows no abnormalities. She fails an initial hearing screen and auditory brainstem response testing.

Ophthalmologic evaluation at 4 weeks of age shows incomplete retinal vascularization, with no evidence of

TABLE 1. Initial Serum Laboratories and Arterial Blood Gas Results

LABORATORY TEST	PATIENT RESULT
White blood cell count	7,200/ μ L (7.2×10^9 /L)
Hemoglobin	13.4 g/dL (134 g/L)
Hematocrit	40.3%
Platelet	29×10^3 / μ L (29×10^9 /L)
Total protein	3.4 g/dL (34 g/L)
Albumin	2.2 g/dL (22 g/L)
Alanine aminotransferase	298 U/L (4.9 μ kat/L)
Aspartate aminotransferase	682 U/L (11.4 μ kat/L)
Alkaline phosphatase	129 U/L (2.1 μ kat/L)
Total bilirubin	5.4 mg/dL (92.3 μ mol/L)
Direct bilirubin	0.9 mg/dL (15.4 μ mol/L)
pH	7.20
Pco ₂	48.4 mm Hg (6.4 kPa)
Po ₂	57 mm Hg (7.6 kPa)
Bicarbonate	18.7 mEq/L (18.7 mmol/L)
Lactic acid	15.65 mmol/L

TABLE 2. Liver Panel, Second Week After Birth

LABORATORY TEST	PATIENT RESULT
Total protein	4.2 g/dL (42 g/L)
Albumin	3.1 g/dL (31 g/L)
Alanine aminotransferase	15 U/L (0.25 μ kat/L)
Aspartate aminotransferase	28 U/L (0.47 μ kat/L)
Alkaline phosphatase	219 U/L (3.6 μ kat/L)
Total bilirubin	1.0 mg/dL (17.1 μ mol/L)
Direct bilirubin	0.4 mg/dL (6.8 μ mol/L)

chorioretinitis or neovascularization. After discharge, repeat examination shows normalization of abnormalities.

DISCUSSION

The differential diagnosis for nonimmune hydrops fetalis (NIHF) includes the following (1):

- Chromosomal abnormalities
- Infectious causes (TORCH infections, parvovirus B19, coxsackievirus)
- Cardiac defects: Structural abnormalities, arrhythmias, high-output heart failure
- Hemolytic and aplastic anemias
- Inborn errors of metabolism
- Placental malformations
- Thoracic, gastrointestinal, or urinary tract defects
- Hepatic disorders such as hepatitis or fibrosis
- Idiopathic

The Condition

NIHF occurs when there is dysregulation of fluid balance between interstitial and vascular spaces, leading to fluid collection in 2 body cavities or tissue with no history of Rhesus iso-immunization. (1) Classic causes of NIHF were ruled out in our patient. Infectious studies and newborn screening results were normal. Abnormalities related to anatomic defects or infection were not present on abdominal or brain imaging. Our report of an HIV-exposed uninfected neonate elucidates the possible relationship between highly active antiretroviral therapy (HAART) exposure and acute liver injury resulting in NIHF.

Evidence on how in utero HAART exposure affects the neonate is incomplete. However, studies have established the role of nucleoside reverse transcriptase inhibitor (NRTI)-related mitochondrial dysfunction, (2) which can lead to lactic acidosis, a striking laboratory finding in our patient. This is caused by NRTI affinity to mitochondrial

DNA polymerase γ and subsequent alterations in the mitochondrial genome, which encode factors needed for aerobic metabolism. Resulting oxidative stress can lead to lactic acidosis and cell injury affecting many organ systems. (2)

The ascites and pericardial effusions in this patient may have been caused by hepatitis resulting in hypoalbuminemia and right ventricular dysfunction. Her acute liver injury was evidenced by elevated serum transaminases, conjugated hyperbilirubinemia, and impaired hepatic synthetic function with hypoalbuminemia and coagulopathy. Once HAART was halted, the infant showed clinical and serologic improvement. Her marked lactic acidosis makes the HAART regimen a likely culprit. Although cardiac dysfunction is a well-documented cause of NIHF, right ventricular dysfunction was not likely responsible here, given that cardiac function and coronary artery size normalized on repeat echocardiography. Instead, the coronary artery abnormality was likely secondary to increased fetal oxygen demand, and not direct cardiomyocyte damage. In addition, evidence of cardiac consequences caused by in utero HAART exposure is incomplete. (3)

Given the clinical improvement, normal liver ultrasound scan, and reversal of the ascites, hepatitis secondary to in utero exposure to HAART therapy is likely the cause. Although there is no way to prove causality between HAART and NIHF in this patient, our case reveals a potential association between these 2 phenomena and demonstrates the need for further evaluation of this relationship.

Lessons for the Clinician

- Nonimmune hydrops fetalis is defined as accumulation of fluid in 2 body cavities with no history of Rhesus incompatibility.
- Established etiologies of NIHF include chromosomal abnormalities, cardiac defects, infection, hematologic disorders, gastrointestinal abnormalities, and inborn errors of metabolism.

- HAART exposure in utero can cause lactic acidosis, and may, in an extreme case, result in hepatic dysfunction leading to NIHF.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of perinatal HIV infection.
- Know the differential diagnosis and the plan of evaluation and management of a fetus with nonimmune hydrops.

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Case 1: Preterm Neonate with Hydrops and Lactic Acidosis

Vibha Szafron, Amir Kazerouninia and Ganga Gokulakrishnan

NeoReviews 2019;20:e520

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Index of Suspicion in the Nursery

2

Rapidly Growing Neck Mass in an Extremely Preterm Infant with Pulmonary Hypertension

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PRESENTATION

A male infant is born at a gestational age of 27 weeks, 4 days via cesarean delivery to a 27-year-old gravida 2, para 1 woman with severe preeclampsia (treated with intravenous magnesium and nifedipine). The pregnancy had been complicated by systemic lupus erythematosus (treated with prednisone and plaquenil) and type 2 diabetes (treated with insulin and aspirin). Second-trimester prenatal ultrasonography at 25 weeks' gestation reveals intrauterine growth restriction with an estimated fetal weight less than the 3rd percentile. At delivery, the infant's Apgar scores are 5 and 8 at 1 and 5 minutes, respectively. He receives positive pressure ventilation, makes a transition to continuous positive airway pressure (CPAP) of 5 cm H₂O, and is transported to the NICU.

During his NICU stay, the infant develops severe bronchopulmonary dysplasia with pulmonary hypertension, apnea and anemia of prematurity, retinopathy of prematurity, failure to thrive, and postnatal growth restriction. Forty-four days after birth, he starts treatment with sildenafil 1 mg/kg per dose every 8 hours for pulmonary hypertension. Fifty-eight days after birth, soft, nonblanching skin-colored nodules develop in both axillae and supraclavicular fossae, but are more prominent on the right side (Fig 1).

An apparent palpable thrill is detected in the axillary lesions, leading to a clinical diagnosis of hemangioma. Of note, there is no laboratory or clinical evidence of consumptive coagulopathy (white blood cell count 8,200/ μ L [8.2×10^9 /L], hemoglobin 9.8 g/dL [98 g/L], hematocrit 31.5%, platelet count 398 $\times 10^3$ / μ L [398×10^9 /L], prothrombin time 12.3 seconds, international normalized ratio 1.2, partial thromboplastin time 36.2 seconds, and fibrinogen 214 mg/dL [2.14 g/L]).

Ultrasonography of the neck (Fig 2) demonstrates an infiltrative echogenic lesion in both axillae containing vessels that demonstrate both arterial and venous flow.

Chest radiography demonstrates no intrathoracic extension and no airway compromise.

Magnetic resonance imaging with contrast is performed to further characterize the axillary masses. It demonstrated slightly enhancing ill-defined lobular axillary lesions extending to the base of the neck.

Given the presumed diagnosis of hemangioma and an observed interval enlargement of the lesions, treatment with propranolol is started. After 3 weeks, no clinical change is noted in the lesions and propranolol is discontinued.

AUTHOR DISCLOSURE Drs Pattnaik, Levin, Gagne, and Angert have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

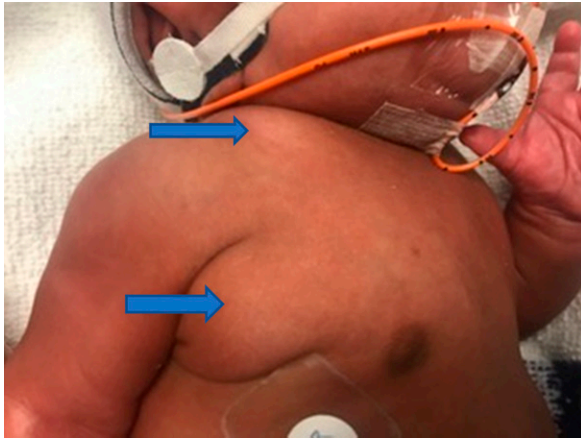


Figure 1. Photograph of the infant demonstrating a right-sided neck mass (arrow). This was present on the left side of the neck as well and extended into the axillae.

A contrast-enhanced computed tomography (CT) scan (Fig 3) reveals prominent low attenuation tissue in the lower neck, supraclavicular region, and axilla bilaterally. No discrete mass is identified and faint postcontrast enhancement is noted. A diagnosis of prominent brown adipose tissue is made.

Echocardiography performed 85 days after birth reveals improved right ventricular pressures with persistent elevation of right ventricular pressure with sildenafil treatment to less than half the systemic pressure. The neonate's respiratory needs improve with progressive weaning of CPAP. On 114 days after birth, he is transferred to an inpatient rehabilitation facility receiving treatment with sildenafil and CPAP 7 cm H₂O, and 23% oxygen for respiratory support. He is weaned off CPAP before discharge 157 days after birth, when he was sent home with nasal cannula oxygen.

DISCUSSION

Brown adipose tissue (BAT) is rich in glycogen, cholesterol, and phospholipids. In contrast to white adipose

tissue, which stores energy, brown fat is involved in nonshivering thermogenesis. (1) This ability is dependent on the expression of uncoupling protein 1 (UCP1), a mitochondrial protein transporter that uncouples electron transport from adenosine triphosphate production. (2) UCP1, which is unique to brown fat, is activated via a signaling cascade triggered by norepinephrine. In humans, brown adipose tissue typically accumulates within the neck, axillae, back, subpleural regions, mediastinum, abdomen, and thigh, and is more abundant in the fetus and neonate, where it may constitute approximately between 1% and 5% of body weight. (3) At 8 weeks after birth, the amount of BAT gradually declines. In adults, it may still be found in the perirenal space, posterior cervical and axillary lymph nodes, and intercostal areas. (4)

In the current case, masslike areas developed, which proved to represent BAT, after treatment with sildenafil for pulmonary hypertension. The relationship between sildenafil and BAT has been previously reported in overweight adults. It has been shown that sildenafil induces the development of brown fat by causing an increase in multilocular UCP1-positive adipocytes and the expression of UCP1 protein and mRNA. Sildenafil also increases mitochondrial density. (5) The mechanism of brown fat induction by sildenafil was proposed by Li et al. (5) Sildenafil increases plasma cyclic guanosine monophosphate and catecholamine, and consequently activates the mammalian target of rapamycin and protein kinase G/vasodilator-stimulated phosphoprotein signaling pathways, respectively, which may be responsible for brown fat activation.

In conclusion, the development of axillary and neck masses in a child with pulmonary hypertension treated with sildenafil should prompt consideration of the diagnosis of brown fat proliferation. Ultrasonography may

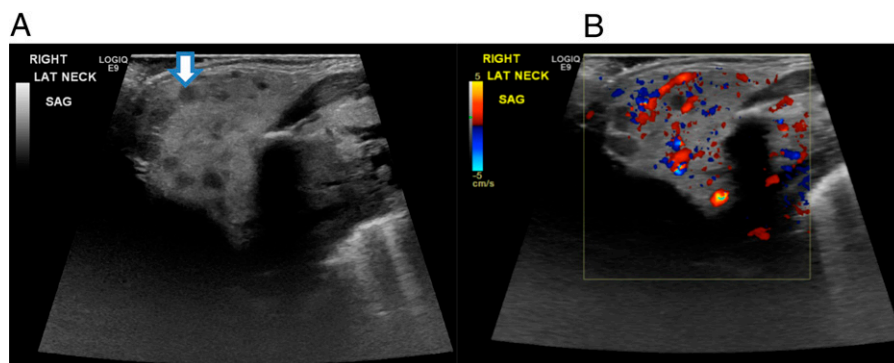


Figure 2. Ultrasound scan of the right side of the neck without (A) and with (B) color Doppler shows an infiltrative echogenic lesion containing multiple rounded hypodense areas (arrow). Doppler image demonstrates prominent vascular flow within the mass.

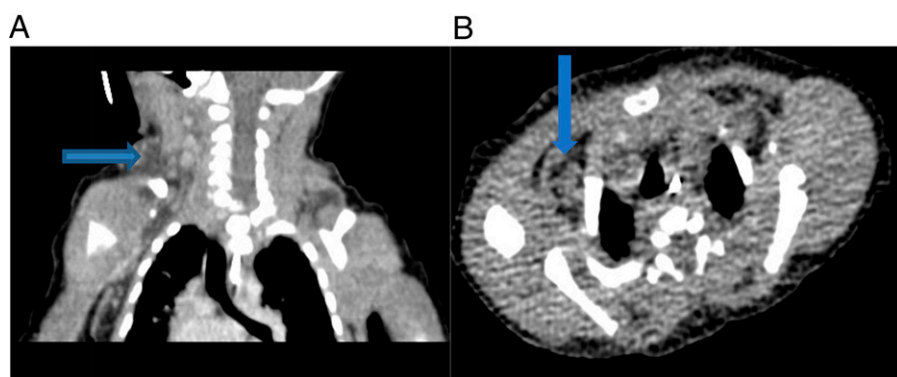


Figure 3. Contrast-enhanced coronal (A) and axial (B) computed tomography scan of the neck shows low attenuation tissue in the lower neck extending to both axillae consistent with fat (arrows). No additional mass was identified.

demonstrate echogenic tissue characteristic of brown fat. Although it was not performed in the current case, positron emission tomography (PET)/CT may be useful in confirming the diagnosis. Radiotracer from PET/CT using fludeoxyglucose Fr18 readily accumulates in sites of metabolically active BAT.

Lessons for the Clinician

- Brown fat proliferation can be associated with sildenafil use in neonates and it is benign.
- Other causes of highly vascular masses in the neck and axilla, such as hemangioma, hemangioendothelioma, and arteriovenous malformations or lipoblastoma should be considered in the differential diagnosis.
- Ultrasonography of the neck is the initial choice of imaging study, and magnetic resonance imaging or positron emission tomography can help confirm the diagnosis in difficult cases.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Normal development of the nose, mouth, throat, and neck.

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Case 2: Rapidly Growing Neck Mass in an Extremely Preterm Infant with Pulmonary Hypertension

Priyam Pattnaik, Terry Levin, Samuel Gagne and Robert Angert

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Index of Suspicion in the Nursery

2 Recurrent Hypoglycemia in Early Neonatal Period

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PRESENTATION

A female neonate is born at 40 weeks of gestation to a primigravida mother via caesarean section for a failed induction. History included second-degree consanguinity, with the mother having hypothyroidism (receiving thyroxine supplementation) and gestational diabetes mellitus (controlled on diet) antenatally. The neonate weighs 2.7 kg at birth, appropriate for gestational age. The postnatal transition is uneventful and she has no gross dysmorphic features. She continues to be exclusively breastfed and is hemodynamically stable throughout. On routine blood glucose monitoring (in view of the mother having gestational diabetes), she is found to have asymptomatic hypoglycemia with a blood glucose level of 36 mg/dL (2 mmol/L). On reexamination, she looks hyperpigmented compared to both her parents (Figs 1 and 2) without any virilization of genitals or hairy pinna. Neurologically she remains normal and abdominal examination does not reveal any hepatosplenomegaly. Her blood glucose remains less than 40 mg/dL (2.2 mmol/L) on multiple occasions in spite of supplemental formula feeds. Therefore she is admitted to the NICU, and is given glucose at a rate of 6 mg/kg per minute. Repeat blood glucose after 1 hour of starting intravenous 10% glucose is 58 mg/dL (3.2 mmol/L) and remains well within the normal range on continuous glucose infusion.

DISCUSSION

Progression

Over the next 1 week, whenever an attempt is made to taper the glucose infusion rate, the infant develops recurrent episodes of hypoglycemia. Investigations are planned with the following differential diagnoses: sepsis, hyperinsulinism, defects of enzymes involved in glycogen storage, gluconeogenesis, fatty acid oxidation pathways, organic acidurias, and defects in hyperglycemic hormones such as glucagon, adrenalin, growth hormone, and cortisol. Normal hematologic indices (hemoglobin 15.3 g/dL [153 g/L], white blood cells 8,200/ μ L [8.2×10^9 /L], and peripheral blood smear normal) and C-reactive protein level excludes sepsis. Serum electrolytes and renal and hepatic function test results are all normal. Urine is negative for ketone bodies and reducing substances, and the insulin (5.2 μ U/mL) to glucose (74 mg/dL) ratio (0.07) is within normal range, thus excluding hyperinsulinism. No metabolic acidosis is seen, and normal lactate and ammonia levels rule out enzyme defects. Later tandem mass spectrometry of blood and gas chromatography mass spectrometry of urine are also reported to be normal,

AUTHOR DISCLOSURE Drs Sharma, Venkatnarayan, and Shaw have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Striking hyperpigmentation in the infant as compared to her mother.

ruling out any inborn errors of metabolism. Investigations for endocrine insufficiency show morning cortisol levels to be less than $0.5 \mu\text{g/dL}$ (13.8 nmol/L) and adrenocorticotrophic hormone (ACTH) levels to be greater than $1,250 \text{ pg/mL}$ (275 pmol/L). So a primary diagnosis of glucocorticoid deficiency is made. The differential diagnosis includes congenital adrenal hyperplasia, which is ruled out because the 17-hydroxyprogesterone level is not raised, there are no signs of hyperandrogenism (no virilization), electrolyte levels are normal, and no evidence of adrenal hyperplasia is noted on ultrasonography and computed tomography (CT) scan of adrenal glands. CT of the adrenal glands also rules out any adrenal hemorrhage, trauma, and infection. Triple A syndrome (adrenal insufficiency, alacrimia, achalasia) is also excluded because the infant has normal esophageal patency.

Diagnosis/Management

Final diagnosis of familial glucocorticoid deficiency (FGD) is made in view of consanguinity, recurrent hypoglycemia, hyperpigmentation, markedly high ACTH levels, and low cortisol without evidence of increased sex steroids, or



Figure 2. Hyperpigmentation of entire skin.

mineralocorticoid deficiency and absence of adrenal hyperplasia. Homozygous stop gain mutation c.T60G (p.Y20X) of Exon 3 (NM_206898) in the *MRAP* gene (Chr21: 33671342), a variant of unknown significance, was detected with Sanger sequencing (Fig 3).

Replacement treatment with hydrocortisone (10 mg/m^2 per day) was started as soon as the diagnosis of glucocorticoid deficiency was made (later changed to oral hydrocortisone 1 mg/kg per day), and there was no more hypoglycemic event. On follow-up until 1 year of age, the infant showed adequate weight gain, with normal neurologic findings.

The Condition

Neonatal hypoglycemia is commonly encountered in neonatal nurseries and NICUs, especially in low-birthweight neonates, including those with intrauterine growth restriction and those with diabetic mothers. (1) Recurrent hypoglycemia is rarer and should be looked for specifically in the presence of other clues noted in the neonate. The brain is almost entirely dependent on glucose for its metabolic needs and recurrent hypoglycemia can restrict brain growth. (2) Hence, it is extremely important to make a timely diagnosis and manage a case of recurrent hypoglycemia to prevent both short- and long-term morbidity and the associated mortality.

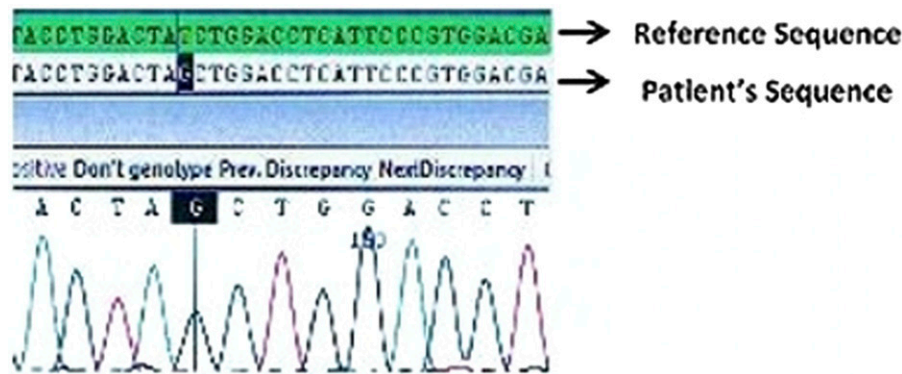


Figure 3. Sanger sequencing showing homozygous stop gain mutation *c.T60G* (*p.Y20X*) of Exon 3 (NM_206898) in the *MRAP* gene.

FGD is a rare autosomal recessive disorder resulting from adrenal unresponsiveness to ACTH. This disease is characterized by low serum cortisol concentrations in the presence of grossly elevated plasma ACTH levels. Affected individuals typically present with recurrent hypoglycemia, hypoglycemic seizures, failure to thrive, recurrent infections, and hyperpigmentation. (3) The severe pigmentation of the skin is caused by the overstimulation of melanocortin 1 receptor (MC1R; cutaneous melanocyte-stimulating hormone [MSH] receptors) by high circulating MSH which is a byproduct of ACTH synthesis from proopiomelanocortin. This hyperpigmentation fades once proper treatment with glucocorticoids is initiated, which reduces ACTH concentrations. (4) Patients with FGD often present in late infancy or adolescence in view of nonspecific signs and symptoms and often after a stressful event. Positive family history of consanguinity, unexplained infant death, or having other affected family members supports the diagnosis. (5) The current patient was severely hyperpigmented at birth, which suggests that the fetal corticotrophs could produce excessive plasma ACTH in response to low fetal cortisol, which in turn, acted on melanocytes before birth.

Lessons for the Clinician

- Recurrent neonatal hypoglycemia is likely to be missed unless looked for specifically in the presence of risk factors.
- Familial glucocorticoid deficiency is an important cause of recurrent neonatal hypoglycemia, though it often

presents in late infancy or adolescence, usually after a stressful event.

- Increased pigmentation is an important clinical clue to the diagnosis of familial glucocorticoid deficiency.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes.

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Case 2: Recurrent Hypoglycemia in Early Neonatal Period
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Index of Suspicion in the Nursery

2 Refractory Respiratory Failure and Pneumothorax in a Full-Term Newborn

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AUTHOR DISCLOSURE Drs Reed, Arya, Dufendach, and Leino have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant with a birthweight of 2,925 g is delivered at 38 6/7 weeks of gestation by a 32-year-old gravida 1, para 1 mother. The pregnancy is uncomplicated, and the mother's evaluation for infection before delivery is negative. The birth occurs via precipitous vaginal delivery and is uneventful except for terminal meconium. At delivery, the infant is initially vigorous with an appropriate heart rate and tone, but she subsequently requires resuscitation because of increased work of breathing and oxygen saturation in the low 60s. She is treated with positive pressure ventilation, and the fraction of inspired oxygen is increased to 100%. Despite positive pressure ventilation, her physical examination findings and oxygen saturation do not improve. Her 1- and 5-minute Apgar scores are 7 each. Initial chest radiography shows a right-sided pneumothorax and pneumomediastinum. Her first capillary blood gas is notable for a pH of 6.9, a partial pressure of carbon dioxide (Pco₂) of 101 mm Hg (13.4 kPa), and a base deficit of 13. Needle decompression of the right chest is attempted, after which the infant is intubated and mechanical ventilation is started. Screening infectious laboratory tests are performed and empirical broad-spectrum antibiotics are started. The infant is then transferred to a tertiary care facility for further care. Upon arrival, the infant is switched to a high-frequency oscillator. At this point, repeat chest radiography shows bilateral pneumothoraces and pneumomediastinum, so bilateral chest tubes are placed.

DISCUSSION

Despite oscillatory ventilation, 100% fraction of inspired oxygen, and surfactant, the infant's oxygen saturation remained in the 80s. An echocardiogram was unremarkable. The capillary gas at 2.5 hours after birth improved slightly, with a pH of 7.03, Pco₂ of 90 mm Hg (12 kPa), and base deficit of 7. Inhaled nitric oxide and inhaled epoprostenol were empirically initiated. Because of persistent hypotension and hemodynamic instability, the infant started treatment with epinephrine and vasopressin, as well as milrinone and hydrocortisone. She had brief clinical improvement, and 8 hours after birth, her capillary gas pH was 7.20, with a Pco₂ of 55 mm Hg (7.3 kPa) and base deficit of 6. However, she progressively deteriorated over the next 24 hours with prolonged oxygen desaturation and hypotension, leading to the initiation of extracorporeal membrane oxygenation (ECMO).

Differential Diagnosis

The infant's initial presentation was concerning for meconium aspiration syndrome with persistent pulmonary hypertension. However, the continued clinical deterioration despite increasing support made this diagnosis less probable. Sepsis was also considered, and the infant was treated with empirical antibiotics, but the lack of improvement despite intervention made this diagnosis less likely as well. Echocardiography ruled out cardiac etiologies such as total anomalous pulmonary vein return, leaving primary pulmonary pathology as the most likely cause for the patient's disease. Persistent respiratory failure requiring continuation of ECMO led to consideration of the diffuse developmental disorders of the lung, including acinar dysplasia (AD), congenital alveolar dysplasia (CAD), and alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV). The differential also included congenital surfactant deficiencies (surfactant protein B deficiency, surfactant protein C deficiency, ABCA3 deficiency).

The Condition

Normal lung development occurs in 5 phases: the embryonic (3–7 weeks after conception), pseudoglandular (5–17 weeks after conception), canalicular (16–25 weeks after conception), sacular (24–36 weeks after conception), and alveolar (36 weeks after conception through adolescence) phases. (1) Lung development can be arrested during any phase, and the timing of the arrest determines the severity of disease. (1) Developmental lung dysplasia was noted as early as 1948 by MacMahon, (2) but because of the rarity of the developmental lung dysplasias, research on the topic is limited, leading to an incomplete understanding of the disease. Incidence and prevalence of the neonatal developmental lung diseases remain unknown, (3) and it remains unclear whether AD, CAD, and ACD/MPV are individual diseases or part of a spectrum of the same disease. (3)

Lung growth arrest during the pseudoglandular or early canalicular phase leads to the diffuse impaired pulmonary acinar development seen in AD. The sacular or alveolar spaces necessary for gas exchange are completely absent, and the lungs may be smaller than expected for the patient's gestational age. Radiologic findings may include hyperinflation, interstitial prominence, and diffuse increased pulmonary density. These patients are typically born at term gestation, and death occurs within hours of delivery. (4) In patients with CAD, lung development is arrested in the late canalicular or early sacular phases. These patients have incomplete alveolarization and absence of secondary

septation, though the lungs are normal in size. Patients with CAD are typically born at term gestation, and death typically occurs in the neonatal period but later than in AD. (5) Disorganized pulmonary maldevelopment during the sacular and alveolar phases leads to ACD/MPV. This condition is associated with defects in the *FOXF1* gene. (6) More than 90% of patients are born at term, and acute hypoxemic respiratory failure develops within 48 hours. (6) Chest radiograph is usually normal but there may be a diffuse ground glass pattern. Although ACD/MPV is also fatal in the neonatal period, 4 known cases presenting as late as 7 months of age are noted in the literature. However, all symptomatic patients have died. (6)

Treatment

Initial therapy for patients with this presentation is supportive. Patients require intubation and potentially ECMO. However, as noted here, these diseases are fatal and to date, there have been no effective life-saving therapies. High-resolution computed tomography may be useful for demonstrating the type of abnormality, extension, and distribution of disease. (4) If a patient is stable with supportive care, a biopsy and genetic testing for the *FOXF1*, *NKX2.1*, *SFTPB*, *SFTPC*, and *ABCA3* genes may be beneficial if lung transplantation is a consideration. (4) In one case, prenatal testing helped avoid escalation to ECMO in a symptomatic patient. (7)

Progression

The infant was given maintenance ECMO for 19 days, during which she developed seizures, and left-sided

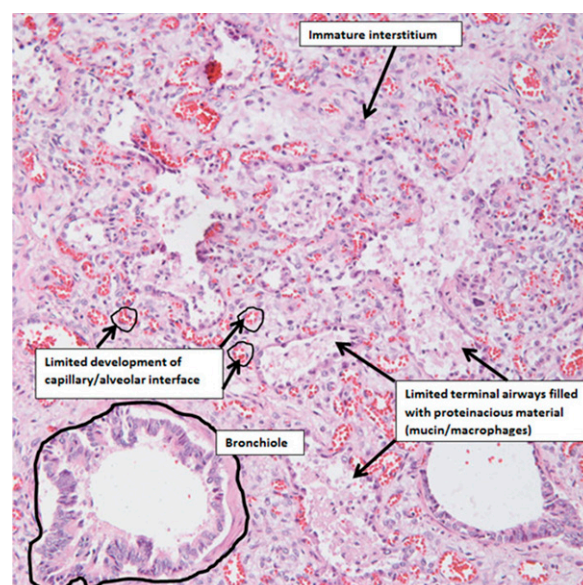


Figure. Hematoxylin-eosin staining of lung tissue obtained in an autopsy of a term infant. Appearance of lungs with histologic maturity is shown at ~23 weeks of gestation. Alveolar development is limited, with persistent interstitium and significant mucus plugging.

parenchymal bleeding was noted. Following ECMO decannulation, the infant had persistent respiratory decompensation for 36 hours, and she died shortly after withdrawal of support with elective extubation on day 24 after birth.

The infant's autopsy findings were consistent with CAD. The lungs were normal in size and weight, but on histopathologic review (Fig), alveolar development was limited and patchy, and intrapulmonary surface area for gas exchange was also limited. This was because of the markedly reduced airspace and persistence of immature interalveolar mesenchyme.

Lessons for the Clinician

- This case highlights the importance of suspecting disorders of lung development and congenital surfactant deficiency in infants with severe and refractory respiratory failure.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the stages and mediators of normal and abnormal cellular and structural development of all components of the lung.

- Know the timing of the biochemical maturation of the lung and the physiological and biochemical factors affecting this timing.

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Case 2: Refractory Respiratory Failure and Pneumothorax in a Full-Term Newborn

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NeoReviews 2018;19:e109

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3 Refractory Seizures Continuing into Infancy in a Term Neonate with Definite History of Perinatal Asphyxia

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PRESENTATION

AUTHOR DISCLOSURE Drs Ramaswamy, Rao, Jalan, and Suryanarayana and Mr Kumar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 7-day-old neonate presents to our NICU with multiple jerky movements of both upper and lower limbs and floppiness. He is the product of a third-degree consanguineous marriage and is born in a peripheral institution. He has a sister who is 6 years old and is healthy.

Birth to 7 Days after Birth

The neonate is born vaginally and requires bag and mask ventilation for 5 minutes. He is transferred to a level II NICU, where he stays for 5 days. He exhibits features of encephalopathy and also has a multifocal clonic seizure 2 hours after birth; he receives a single loading dose of phenobarbital. He is diagnosed as having hypoxic-ischemic encephalopathy (HIE) grade 2. Subsequently, his sensorium improves and he is discharged while breastfeeding exclusively. Since day 6, he has been having multiple episodes of multifocal clonic seizures and is brought to our NICU on day 7.

Day 7 to Day 23

A strong suspicion of neurometabolic disorder arises in view of consanguinity and refractory seizures. He is nil per os. He requires full loading doses of anti-epileptic drugs (AEDs) phenytoin and phenobarbital, after which his seizures stop. Testing for blood glucose, arterial lactate, pH, serum ammonia, urine ketones, and urine-reducing substances and tandem mass spectroscopy for inborn errors of metabolism such as aminoacidopathies and fatty acid oxidation defects all have normal results. Lumbar puncture reveals no meningitis. Magnetic resonance spectroscopy shows hypoxic-ischemic changes. Amplitude integrated electroencephalography (EEG) shows periodic epileptic waveforms with a normal interictal background pattern. Electrographic seizure control is noted after phenytoin loading. Urine and cerebrospinal fluid (CSF) pipelicolic acid levels are elevated. Pipelicolic acid level in CSF is 13.16 $\mu\text{mol/L}$ (reference range, 0.01–2.00 $\mu\text{mol/L}$), and in urine is 451.75 $\mu\text{mol/mmol}$ of creatinine (reference range, 0.55–24.1 $\mu\text{mol/mmol}$ of creatinine). Pipelicolic acid levels are estimated using gas chromatography/mass spectrometry with the selective ion monitoring method using full calibration for both the substances. The neonate receives oral pyridoxine at 30 mg/kg per day in 3 divided doses. EEG changes normalize in the next

24 hours, sensorium improves, and other AEDs are discontinued in the next 3 days. The neonate is discharged on day 23.

Day 45 to Day 52

The neonate experiences seizures again on day 45. Further evaluation reveals CSF 5-methyl tetrahydrofolate (5-MTHF) levels to be very low (10.04 nmol/L; reference range, 60-129 nmol/L). CSF 5-MTHF levels are estimated using ultra high-performance liquid chromatography with fluorescent detector (Fig). After folinic acid supplementation, the seizures

stop. Presently he is 5 months old, undergoing follow-up evaluations, and receiving pyridoxine and folinic acid treatment. His current developmental age is 3 months with global developmental delay being noted.

DISCUSSION

This was a classic case of folinic acid-responsive seizures (FARS), which are biochemically and genetically similar to pyridoxine-dependent epilepsy (PDE). (1) The initial

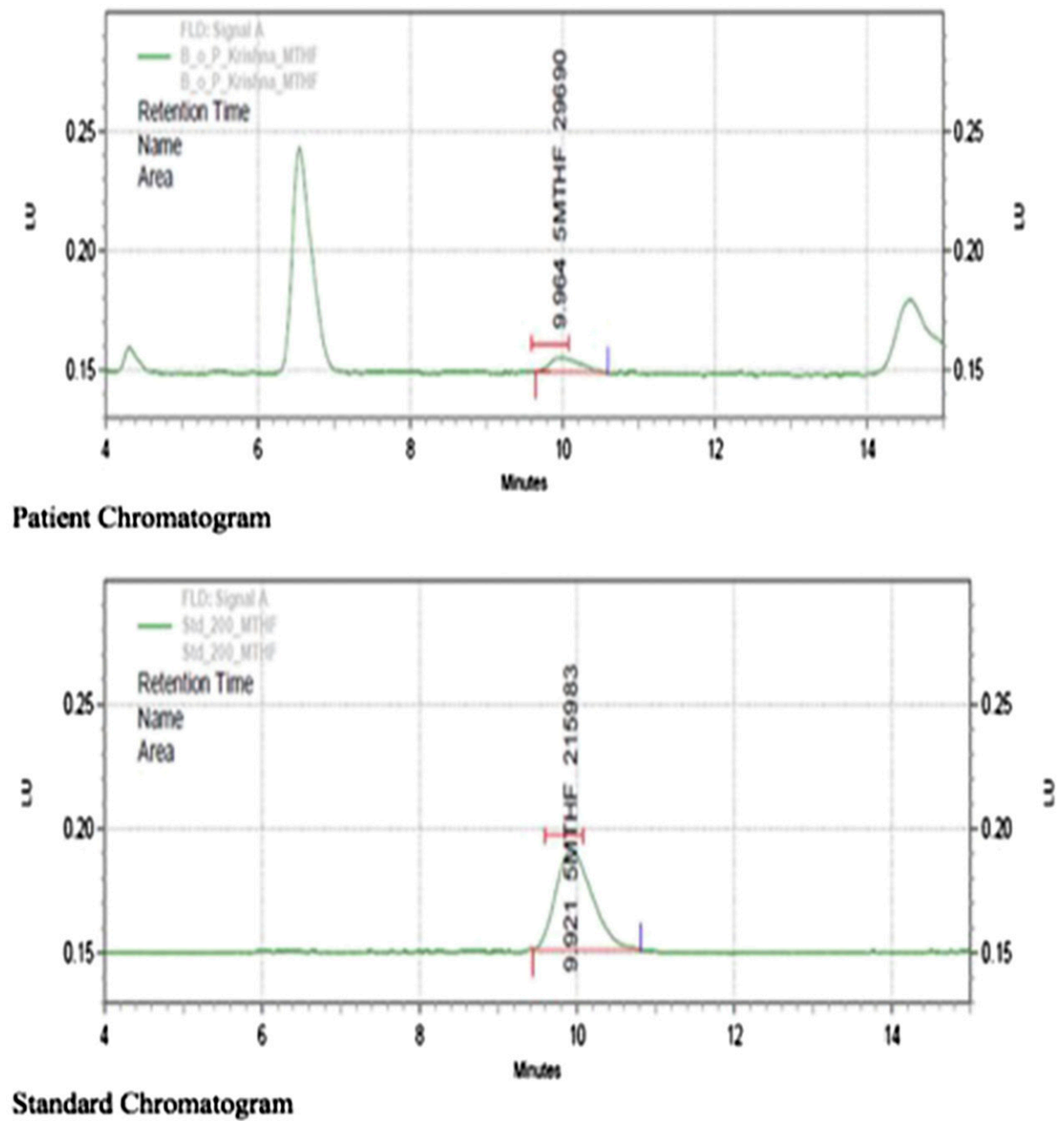


Figure. Cerebrospinal fluid 5-methyl tetrahydrofolate levels, as estimated using ultra high-performance liquid chromatography.

diagnosis was HIE, which was later changed to PDE. Despite extensive investigations, as well as the fact that the neonate was symptomatic since day 1 after birth, the final diagnosis of FARS was made 45 days after birth. This demonstrates the difficulty in making a rapid diagnosis in cases of PDE and FARS.

First Diagnosis

The first diagnosis of HIE grade 2 was relatively straightforward. The fact that the first seizure responded to a single loading dose of phenobarbital was not surprising because PDE has a varied presentation and can respond to AEDs. Also, PDE can mimic asphyxia. (2) To our knowledge, FARS mimicking asphyxia has not been reported in the literature.

Second Diagnosis

The second diagnosis of PDE was made after the urine and CSF pipelicolic acid were found to be elevated. The clinical and electrographic response of seizures confirmed the diagnosis of PDE. In a case report of FARS by Gallagher et al, all of their patients were identified in the neonatal period, 1 responded completely to pyridoxine, 1 had a partial response, and 1 had an initial response followed by recurrence, as seen in the current case. (3) Almost all of them achieved seizure control after folinic acid supplementation.

Final Diagnosis

The final diagnosis of FARS was made after the CSF 5-MTHF levels were measured. The full response to folinic acid supplementation further confirmed the diagnosis.

FARS and PDE are 2 easily treatable neurometabolic conditions that present in the neonatal period. (4) FARS was first reported in 1995 and many case reports were subsequently published. (5) The biochemical and genetic abnormality is exactly the same as that of PDE. The only additional abnormality is the CSF folate deficiency. The mechanism resulting in this folate deficiency in PDE is unknown. This should not be confused with other congenital folate deficiency disorders in which the other biochemical abnormalities of PDE, such as high pipelicolic and α -aminoadipic acid levels in CSF and urine, will not be present. (6) Also, these congenital abnormalities of folate deficiency are not known to present in the neonatal period. The long-term prognosis of PDE and FARS is poor, even in treated cases, but delay in supplementation can only make it worse. (3)

Lessons for the Clinician

- Pyridoxine-dependent epilepsy (PDE) and folinic acid-responsive seizures (FARS) can masquerade as perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE). A high degree of suspicion should be maintained in a neonate with HIE who has breakthrough seizures in the neonatal and early infancy period, because seizures related to HIE resolve during this period.
- All cases of suspected neurometabolic disorders should be evaluated for both FARS and PDE. Folinic acid supplementation along with pyridoxine supplementation should be used in all suspected cases until definitive reports are available.
- Partial response to pyridoxine supplementation or recurrence in an already diagnosed case of PDE warrants the addition of folinic acid until cerebrospinal fluid 5-methyl tetrahydrofolate levels are available.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Differentiate asphyxia from other causes of depression at birth, including drug effects and hypovolemia.

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**Case 3: Refractory Seizures Continuing into Infancy in a Term Neonate with
Definite History of Perinatal Asphyxia**
Viraraghavan Vadakkencherry Ramaswamy, Gajanan Venkat Rao, Anil Jalan, Nori
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**Case 3: Refractory Seizures Continuing into Infancy in a Term Neonate with
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Index of Suspicion in the Nursery

2 Respiratory Distress and Chronic Aspiration

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PRESENTATION

AUTHOR DISCLOSURE Drs Seske, Prosser, and Haberman have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

A gravida 6, para 4 mother presents with spontaneous labor at 37 1/7 weeks' estimated gestational age (EGA). The pregnancy is uncomplicated, but ultrasonography reports polyhydramnios. Delivery occurs via repeat cesarean section. Copious oral secretions and significant work of breathing are noted at delivery, requiring positive pressure ventilation and intubation of the newborn. The patient undergoes extubation a few days after birth and is weaned to room air. Oral feeds are attempted after extubation, but choking and gagging occur. The care team discusses possible differential diagnoses, such as esophageal atresia/tracheoesophageal fistula (TEF), esophageal webs, esophageal strictures, esophageal diverticulum, tubular esophageal duplications, congenital short esophagus, and tracheal agenesis/atresia. During an upper gastrointestinal series, the patient has bradycardia and desaturations. The study images are interpreted as an H-type TEF. A gastrostomy tube is placed to decompress the stomach, and nutrition is provided via total parenteral nutrition (TPN). The patient is also found to have a horseshoe kidney and an atrial septal defect. Microarray of chromosomes is normal.

The patient continues to require numerous modes of ventilatory support including high-flow nasal cannula and reintubation. Because of a lack of improvement in respiratory status despite providing standard care for a TEF, the team investigates the patient's anatomy more thoroughly. Bronchoscopy shows a large defect that connects the esophagus and larynx. The first attempt at tracheoplasty/esophagoplasty is performed via a lateral thoracotomy approach, but is ultimately unsuccessful. The patient returns to the operating room (OR), where a breakdown of the repair site and a blind pouch are noted on bronchoscopy between the carina and native esophagus. After this procedure, the patient is transferred to our institution for a second opinion.

DISCUSSION

Upon arrival, bronchoscopy confirmed the diagnosis of a laryngotracheal-esophageal cleft extending to 1 cm above the carina and a blind pouch, into which the endotracheal tube (ETT) frequently slipped, causing difficulty providing ventilation (Figs 1 and 2). The patient was sedated intravenously to maximize security of this critical airway and ETT while an operative approach was planned. The patient underwent a median sternotomy for access to the distal trachea and cardiopulmonary bypass. Because of the thrombi in the right internal jugular vein and femoral vein, the patient was not a candidate for extracorporeal

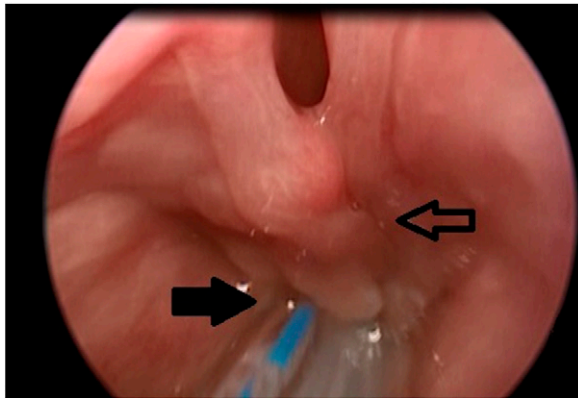


Figure 1. Close-up view of the posterior larynx showing redundant mucosa filling the cleft (outlined arrow). Of note, both the nasogastric tube (blue lines on the left) and the endotracheal tube (on the right) appear to enter the esophagus (solid arrow). The endotracheal tube later enters the trachea through the inferior aspect of the cleft to sit just above the carina.

membrane oxygenation (ECMO). The cleft was repaired by separating the airway at the cricotracheal junction. The esophagus was then closed primarily followed by tracheal closure. A tibial periosteal graft was used as an interposition to prevent breakdown. The trachea was then reattached at the cricoid.

Differential Diagnosis

A laryngeal or laryngotracheoesophageal (LTE) cleft is a congenital malformation of the posterior part of the larynx, creating an abnormal communication between the laryngo-tracheal axis and the pharyngoesophageal axis. The anatomic and physiologic separation between the digestive tract

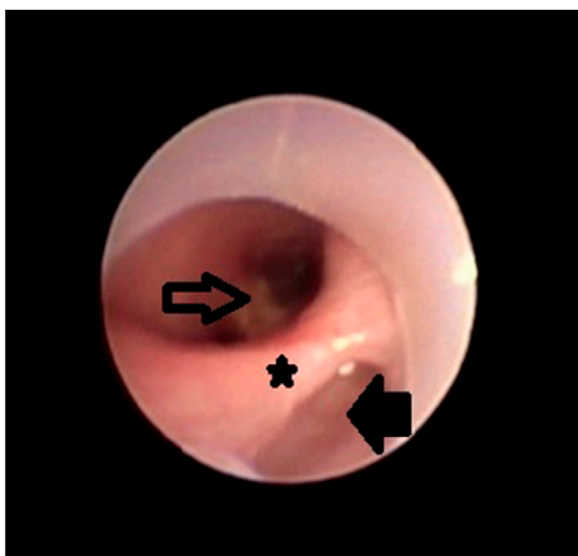


Figure 2. View from within the endotracheal tube showing the carina (outlined arrow), right and left mainstem bronchi as well as the distal aspect of the cleft (star) with the esophagus (solid arrow) posteriorly.

and airway is absent. (1) The severity of the cleft ranges from a mild and sometimes asymptomatic defect of the interarytenoid musculature to a severe, life-threatening cleft extending down past the carina. The severity and symptoms are directly correlated to the caudal extension of the cleft. LTE clefts are estimated to occur in 1 in 10,000 to 20,000 live births. (2) These defects make up 0.2% to 1.5% of congenital malformations of the larynx. (3) Many believe the incidence is underestimated because some mild types are asymptomatic whereas some severe types result in death before evaluation occurs. Richter first reported a clinical case of LTE cleft in a newborn with recurrent aspiration in 1792. (4) Boys have a 2 to 1 higher incidence than girls. (2) Cases are typically sporadic.

Laryngeal clefts are created because of premature arrest in the development of the tracheoesophageal septum, lack of fusion of lateral parts of cricoid cartilage, and/or a disruption resulting in apoptosis. (5) Laryngeal clefts have been reported as part of several syndromes and also occur with associated malformations, including abnormal intestinal rotation, microgastria, hypospadias, renal malformations, coarctation of the aorta, cleft lip, and palate. (1)

Rigid bronchoscopy in the OR under general anesthesia is the gold standard to diagnose laryngeal clefts and can also evaluate for the presence or absence of synchronous airway lesions. In some cases, the posterior glottis must be palpated to evaluate for clefts, because redundant mucosa can prolapse into the cleft, making diagnosis difficult. (6) The most frequently used classification system is that of Benjamin and Inglis. (7) This classification ranges from type 0, which is a submucosal cleft, to type IVb, which is a cleft extending into 1 mainstem bronchus.

Treatment

The first reported successful LTE cleft reconstruction was performed in 1955. (8) High-grade type IV clefts have been reported to require a combined cervical and thoracic approach with cardiopulmonary bypass or ECMO. (9) Extensive clefts should be closed in a layered fashion to minimize the risk of reopening. Interposition grafts are helpful and can be harvested from multiple sites. The tibial periosteum and sternal perichondrium are preferred at our institution because of the ease of harvest, manipulation, and healing.

Because of the rarity of the disease, data on long-term outcomes of severe type IV LTE clefts are limited. Many patients require tracheostomy due to tracheomalacia, feeding via gastrostomy tube due to feeding intolerance or oral aversion, and numerous rounds of antibiotics due to pulmonary infections. Up to 50% of cases require

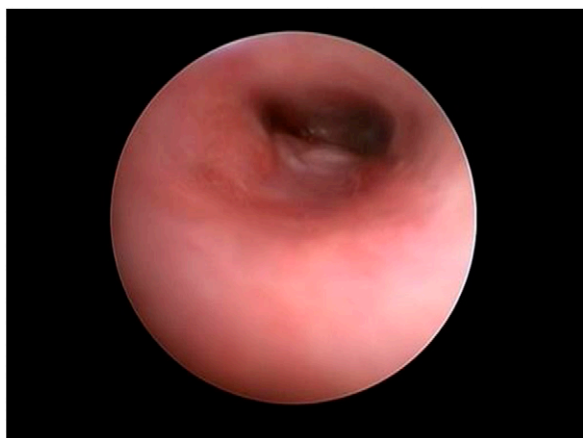


Figure 3. Repaired cleft 6 months later showing an intact posterior tracheal wall down to the carina without evidence of dehiscence.

revision due to reopening of the cleft in the postoperative period. (10) As a result of these challenges, the mortality rate for type IV laryngeal clefts was 93% in 1983. (11) With advancements in our surgical approaches and postoperative care, in 2010, the mortality rate dropped to 50% to 75%. (12) This continues to remain high in part because of other congenital anomalies that are often present in this population. Complicating factors (such as extremity thrombosis preventing ECMO in our patient) are frequently present in this patient population, requiring a coordinated team approach to adequately identify and manage. Patients are also at risk for developmental delays because of a complicated and lengthy medical course.

Progression

After surgery, the patient described herein was treated with numerous intravenous infusions of sedatives, diuretics for fluid management, TPN, and anticoagulation prophylaxis. The patient required an emergent trip to the OR because of a mucous plug in the ETT, which necessitated replacement. After bronchoscopy confirmed healing of the repair site, a tracheostomy was performed to manage the severe tracheomalacia that is expected after type IV LTE cleft repairs. The patient was then weaned off the ventilator to a tracheostomy collar and cool mist. The patient completed several courses of antibiotics for aspiration pneumonia and tracheitis. Follow-up ultrasonography showed resolution of the extremity clots and the patient continued to receive enoxaparin sodium for prophylaxis. Lansoprazole was started postoperatively to protect the repair site from potential gastroesophageal reflux and was continued after discharge. The patient was discharged with gastrostomy tube feedings. Follow-up with repeat bronchoscopies revealed an intact stable repair at age 6 months (Fig 3).

Lessons for the Clinician

1. Laryngeal clefts are rare congenital malformations of the airway and should be considered in patients with signs and symptoms of respiratory distress and chronic aspiration.
2. Although survival rates for laryngeal clefts have improved because of advances in surgical approaches, they still remain low because of the extensive complex treatment required.

American Board of Pediatrics Neonatal—Perinatal Content Specification

- Know the various types and diagnostic features of tracheoesophageal fistulae and esophageal atresias

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Case 2: Respiratory Distress and Chronic Aspiration

Laura M. Seske, J. Drew Prosser and Beth E. Haberman

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Index of Suspicion in the Nursery

3 Respiratory Distress and Tachycardia in a Preterm Neonate

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Rachel G. Greenberg, MD, MHS,[‡] Stephanie Burns Wechsler, MD,*[§]
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PRESENTATION

A 31-week-gestation male infant is delivered vaginally in the setting of preterm labor and chorioamnionitis. The pregnancy was remarkable for late prenatal care, but no other complications. Maternal antenatal testing results were normal and the mother denied any significant medical history. The infant is initially stunned, but quickly recovers, with Apgar scores of 1 and 7 at 1 and 5 minutes, respectively. His size is appropriate for gestational age and his vital signs in the intensive care nursery include a temperature of 98.8°F (36.5°C), pulse of 172 beats/min, right lower extremity blood pressure of 76/34 mm Hg, respiratory rate of 62 breaths/min, and oxygen saturation of 98% on nasal continuous positive airway pressure support at 5 cm H₂O and 21% fraction of inspired oxygen. On examination, the infant's anterior fontanelle is soft, flat, and approximately 1 fingertip in size. His lungs are clear despite a mildly increased respiratory effort, including grunting and subcostal retractions. He has normal first and second heart sounds, a gallop rhythm, and no murmurs, and his liver is palpable 4 cm below the right costal margin.

On investigation, chest radiography demonstrates an enlarged cardiac silhouette (Fig 1), and echocardiography shows findings consistent with restrictive cardiomyopathy, normal systolic function, but impaired diastolic function (Fig 2). Given this rare finding, pediatric cardiology is consulted, which recommends conducting a comprehensive cardiomyopathy genetic testing panel. During his first week after delivery, the infant develops frequent ventricular ectopic beats and mild hypotension, necessitating volume resuscitation. His baseline heart rate shows a higher trend, toward a mean of 200 beats/min, and his tachycardia fails to respond to multiple fluid boluses. The team is also unable to wean him off the respiratory support. A milrinone infusion is started to relax the myocardium and augment cardiac output.

DISCUSSION

Given the infant's persistent tachycardia, thyroid disease is considered and evaluated. The thyrotropin level is decreased at 0.01 μ IU/mL (normal, 0.34–5.66 μ IU/mL) and the levels of total triiodothyronine (total T₃) and free thyroxine (fT₄) are markedly elevated (280 ng/dL [4.3 nmol/L; normal, 80–178 ng/dL,

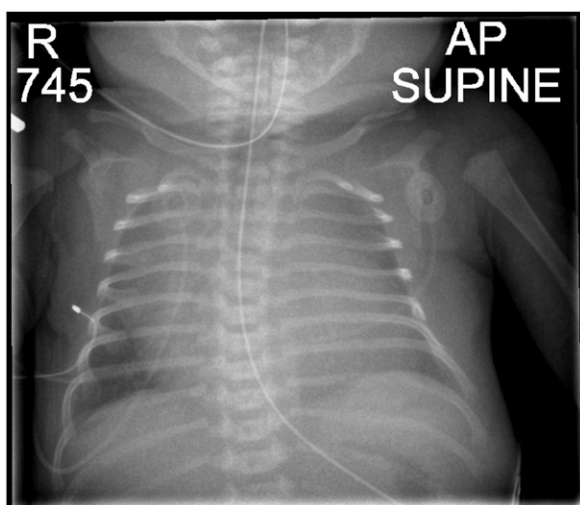


Figure 1. Chest radiograph demonstrating enlarged cardiac silhouette obscuring lung fields.

1.2–2.7 nmol/L) and 5.83 ng/dL [75 pmol/L; normal 0.52–1.21 ng/dL, 6.7–15.5 pmol/L], respectively). Although his mother again denies medical problems, the team suspects neonatal Graves disease and starts methimazole and propranolol.

The infant's heart rate normalizes on treatment for hyperthyroidism and he quickly weans off respiratory support and milrinone (Fig 3). Repeat echocardiography demonstrates improving diastolic function. Interestingly, the comprehensive cardiomyopathy panel returns with a mutation in the *RYR2* gene. Mutations in the *RYR2* gene have been associated with increased risk of developing catecholaminergic polymorphic ventricular tachycardia as well as arrhythmogenic right ventricular cardiomyopathy. However,



Figure 2. Apical 4-chamber echocardiogram demonstrating enlarged right and left atria bilaterally.

the results of a functional analysis show that this infant's mutation is unlikely to have clinical significance.

Before discharge, propranolol is discontinued and the infant's diastolic function and chamber sizes completely normalize. His mother is found to have active Graves disease and a goiter that has been covered by scarves and clothing with high necklines. The infant's methimazole is discontinued at 5 months of age and he has not had any further thyroid dysfunction.

The Condition

Neonatal Graves disease is a rare disorder that occurs when maternal thyrotropin receptor antibody (TRAb) crosses the placenta to reach the fetus. The estimated incidence of neonatal Graves disease is 1 in 25,000 to 50,000; only 0.2% of pregnant women have Graves disease and only 1% to 5% of their infants develop neonatal hyperthyroidism. (1)(2) Clinical manifestations of neonatal Graves disease include irritability, hyperactivity, flushing, poor weight gain, tachycardia, hyperthermia, diarrhea, frontal bossing, triangular facies, small anterior fontanelle and less commonly, heart failure, exophthalmos, cholestasis, thrombocytopenia, and hyperammonemia. (1)(2)(3)(4) A goiter is another sign of neonatal Graves disease, but can be difficult to detect in neonates. Therefore, thyroid ultrasonography should be used in suspected cases. (5) While reversible dilated cardiomyopathy can be seen in thyrotoxicosis, restrictive cardiac physiology, as was seen in this case, has not been described previously. (6)

Diagnosis

The timing of neonatal symptom development depends on the mother's use of an antithyroid medication such as methimazole. In the case of untreated mothers, including those who have had thyroidectomies or radioactive iodine ablation, the neonate may be symptomatic at birth and have abnormal thyroid function tests within the first week after delivery. (5) Conversely, infants born to mothers taking antithyroid medications may not manifest symptoms until 1 to 3 weeks after birth because of the drug's ability to cross the placenta. Importantly, infants with neonatal Graves disease may be euthyroid on the state newborn screen.

Laboratory evaluation can assist in the diagnosis and help predict the clinical course. Thyroid stimulating index assays specifically detect the presence of stimulating antibodies by measuring cyclic adenosine monophosphate production. (7) TRAb assays are competition-based, meaning they detect the presence of TRAb but cannot distinguish between stimulating, blocking, and neutral antibodies. (7) A negative TRAb finding in an infant is reassuring against future

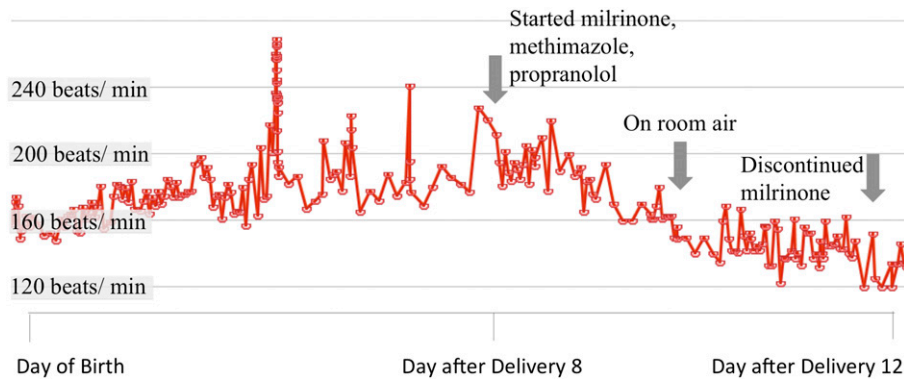


Figure 3. Heart rate trend from birth to 12 days after delivery.

development of neonatal Graves disease, and these infants can have standard pediatric care without additional thyroid monitoring. (5) Not surprisingly, high maternal serum TRAb levels late in pregnancy increase the likelihood that an infant will develop neonatal Graves disease. (5)

Management

Infants with neonatal Graves disease are commonly treated with a β -blocker and an antithyroid medication. (3) Methimazole is the preferred pediatric antithyroid agent because propylthiouracil carries a black box warning for hepatotoxicity. (8) More severe cases of neonatal Graves disease may require iodine (Lugol solution) to inhibit thyroid hormone release and/or glucocorticoids to reduce the conversion of fT_4 to the more active T_3 . (9)(10)

Infants with neonatal Graves disease should be closely followed by a pediatrician and pediatric endocrinologist to monitor weight gain and thyroid function tests. Maternal TRAb levels in the infant typically wane between 3 and 12 weeks, and in most infants, the disease resolves spontaneously during this period, allowing methimazole to be discontinued. (1) The transient nature of neonatal Graves disease should be emphasized to parents because frequent laboratory evaluations are necessary to ensure that the infants do not become hypothyroid with methimazole treatment.

Lessons for the Clinician

- Vital sign abnormalities may be the first indicator of underlying thyroid disease.
- Neonatal Graves disease can present various phenotypes. Cardiac manifestations may be tachycardia alone, but evidence of cardiomyopathy (dilated or restrictive) is possible.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the anatomy and pathophysiology (including genetics) of an infant with a condition affecting myocardial performance.
- Identify the etiology, clinical manifestations, laboratory features, and management of neonatal thyrotoxicosis.

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Case 3: Respiratory Distress and Tachycardia in a Preterm Neonate
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Index of Suspicion in the Nursery

1 Scrotal Swelling in a Term Infant

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AUTHOR DISCLOSURE Drs Alallah, Sulaiman, and Khattab have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant is born at 39 weeks' gestation via vacuum-assisted vaginal delivery due to fetal deceleration to a 37-year-old gravida 3, para 2 woman. The woman's pregnancy had been uncomplicated. Antenatal ultrasonography findings had been normal. The infant's birthweight is 3,755 g. The newborn was given a vitamin K injection at the time of birth. He is sent to the normal nursery with his mother in good condition; at 8 hours after birth, the mother notes that the infant has right scrotal swelling. He is transferred to the NICU for further evaluation and treatment.

The infant is stable on room air, with a temperature of 36.8°C, heart rate of 150 beats/min, respiratory rate of 55 breaths/min, and oxygen saturation of 94%.

On physical examination, he has no pallor and displays no irritability. The examination shows no evidence of skin bleeding or stigmata of congenital infection. There is no significant organomegaly on abdominal examination, and the rest of the systemic examination findings are within normal limits. Nontender bilateral scrotal swelling is noted to be more pronounced on the right (Fig 1), the swelling did not transilluminate, and the left testis is palpable. No bruising is seen on the groin initially. Abdominal examination findings are normal. There is no evidence of trauma.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute scrotal swelling in newborn includes the following:

- Testicular torsion
- Hydrocele
- Inguinal hernia
- Adrenal hemorrhage
- Birth trauma
- Scrotal hematoma

CASE PROGRESSION

On admission to the newborn nursery, an acute scrotum is initially suspected. Urgent scrotal ultrasonography showed both testes to be normal in their positions, sizes, and outline. A right scrotal fluid collection with minimal free hydrocele was seen with high-level echoes on scrotal ultrasound. No solid or cystic focal lesions were noted, and there was no evidence of testicular torsion. The abdominal ultrasonography findings were normal. Pediatric surgery was consulted, and the patient received conservative management.



Figure 1. Infant with bilateral scrotal hematoma, which is more pronounced on the right, 2 days after birth.

Complete blood cell counts were as follows: platelets, $45 \times 10^3/\mu\text{L}$ ($45 \times 10^9/\text{L}$); hemoglobin, 13.5 g/dL (135 g/L), white blood cells, $15,000/\mu\text{L}$ ($15 \times 10^9/\text{L}$); hematocrit, 38%; and C-reactive protein, 1.5 mg/L (14.3 nmol/L). A platelet transfusion (10 mL/kg) was given. The platelet count after 1 hour was $30 \times 10^3/\mu\text{L}$ ($30 \times 10^9/\text{L}$), with a blood film of severe thrombocytopenia, hemoglobin of 10 g/dL (100 g/L), hematocrit of 28.4%, and white blood cell count of $13,000/\mu\text{L}$ ($13.9 \times 10^9/\text{L}$). A second transfusion of platelets (10 mL/kg) was given and repeat platelet count after 1 hour was $129 \times 10^3/\mu\text{L}$ ($129 \times 10^9/\text{L}$). Coagulation profile showed a prothrombin time of 15.8 seconds (normal 10–14 seconds), international normalized ratio of 1.4 (normal 0.01–1.24), and activated partial thromboplastin time of 41.2 seconds (normal 24–41 seconds). The infant was given nothing by mouth and only intravenous (IV) fluids. Partial evaluation for sepsis was performed, and IV antibiotic treatment with ampicillin and gentamycin was started. Transcranial ultrasonography of the brain had normal findings. Screening for toxoplasmosis, other agents, rubella (also known as German measles), cytomegalovirus, and herpes simplex was negative.

Pediatric hematology was consulted and IV immunoglobulin (1 g/kg) was given on 2 consecutive days for possible neonatal alloimmune thrombocytopenia (NAIT). On day 3 after birth, bluish discoloration was more prominent in the right inguinal area (Fig 2), so a repeat ultrasonography with renal Doppler was performed of the abdomen and pelvis, with normal findings and no evidence of adrenal hemorrhage. Daily complete blood cell count showed improving thrombocytopenia range ($86 \rightarrow 79 \rightarrow 105 \rightarrow 111 \times 10^9/\text{L}$).

The infant remained stable with no evidence of active bleeding. Blood culture was negative. After completing a 5-day course of antibiotics, he was discharged on the sixth day after birth in stable condition with a platelet count of



Figure 2. An extension of right scrotal hematoma in the right inguinal area, 3 days after birth.

$111 \times 10^3/\mu\text{L}$ ($111 \times 10^9/\text{L}$) and improvement in the scrotal hematoma (Fig 3). A follow-up appointment was scheduled with hematology on discharge.

A follow-up visit 48 hours after discharge showed normal platelet count of $147 \times 10^3/\mu\text{L}$ ($147 \times 10^9/\text{L}$), with significant improvement in scrotal swelling. One week later, his platelet count was $495 \times 10^3/\mu\text{L}$ ($495 \times 10^9/\text{L}$), and in the third week a follow-up visit to the clinic showed complete resolution of the swelling (Fig 4).

ACTUAL DIAGNOSIS

The patient was diagnosed as having scrotal hematoma secondary to NAIT.



Figure 3. Just before discharge from the NICU, 6 days after birth.

DISCUSSION

Acute scrotal hematoma in the neonatal period is a rare condition that requires prompt diagnosis and possible urgent intervention. It commonly results from testicular torsion, adrenal hemorrhage, and birth trauma. (1) A few other cases of neonatal scrotal hematoma have been documented in the literature including spontaneous idiopathic hemorrhage of the scrotum. (2)

Our patient presented with acute scrotal swelling, which was thought to be testicular torsion and was excluded on scrotal ultrasonography. The swelling did not transilluminate as would be expected in the case of congenital hydrocele. There was no clinical feature suggestive of trauma. Abdominal ultrasonography excluded the adrenal hemorrhage as a cause of hemoscrotum.

Thrombocytopenia is defined as a platelet count less than $150 \times 10^3/\mu\text{L}$ ($150 \times 10^9/\text{L}$); severe neonatal thrombocytopenia occurs when the platelet count is less than $50 \times 10^3/\mu\text{L}$ ($50 \times 10^9/\text{L}$) and has been associated with significant bleeding such as intracranial hemorrhage. (3)

NAIT is the most common cause of thrombocytopenia in a full-term infant and resolves within 1 week. (4) This is attributed to immune-mediated destruction of fetal and neonatal platelets, and was seen in our case. The unusual presentation of our

case was that of isolated scrotal hematoma with no petechial rash or other significant bleeding on screening ultrasonography. We treated our case with platelet transfusions and IV immunoglobulin because his platelet count was less than $50 \times 10^3/\mu\text{L}$ ($50 \times 10^9/\text{L}$) with a significant scrotal hematoma.

The ideal treatment for a neonate with NAIT is to provide HPA-1a-negative and 5b-negative platelets from the blood bank. But it was not available so random donor platelets were given, which was effective. Maternal platelets can only be used if they are washed because circulating antibodies will also be present.

It is important to consider a broad differential diagnosis in cases of acute scrotal hematoma including thrombocytopenia in the absence of other bleeding site or skin manifestation.

Lessons for the Clinician

- Acute scrotal hematoma in the neonatal period is a rare condition that requires prompt diagnosis and possible urgent intervention.
- Scrotal hematoma most commonly occurs because of testicular torsion, adrenal hemorrhage, birth trauma or thrombocytopenia.
- Neonatal alloimmune thrombocytopenia is the most common cause of thrombocytopenia in a full-term infant and may be a cause of scrotal hematoma.



Figure 4. Clinic visit 4 weeks after birth.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.

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Index of Suspicion in the Nursery

1 Seizures and Rashes Do Run in the Family

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AUTHOR DISCLOSURES Drs Hochberg, Foldi, Nadir, Mahajnah, Shreter, and Feldman have no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term female infant is born by spontaneous delivery at 40 2/7 weeks' gestational age with a birthweight of 3,560 g (50th percentile) and a head circumference of 34.5 cm (50th percentile) to a 25-year-old primigravida. The parental history and the course of the present pregnancy are unremarkable. The infant is born by spontaneous normal vaginal delivery. Her Apgar scores are 8 and 10 at 1 and 5 minutes, respectively. At the age of 43 hours, tonic-clonic movements of the right hand and leg are observed, during which she is completely conscious. The physical examination reveals an erythematous rash on the lower abdomen and lower limbs, which appear and fade (Fig 1), and a small area of alopecia on the right parietal side of the head (Fig 2). The rest of the physical examination findings are normal. Under a presumed diagnosis of neonatal seizures, both basic and extended investigations are undertaken, including infectious, metabolic, hematologic, and endocrinologic tests. Broad-spectrum antibiotics and acyclovir are initiated. The focal seizures worsen, become generalized, and are accompanied by episodes of apnea, deep desaturation, and bradycardia. They cease after second-line levetiracetam is added to the initial phenobarbital treatment. A single dose of pyridoxine (vitamin B6) is also given, with no change in the clinical condition.

The complete blood cell count and the C-reactive protein levels are normal, as are the blood and cerebrospinal fluid (CSF) chemistries. Blood gases, basic and extended metabolic studies, liver function, thyroid function, and a coagulation study are all normal. All cultures are negative. A CSF analysis is negative for a viral panel.

Electroencephalography shows diffused epileptiform activity, especially above the right hemisphere. A brain magnetic resonance imaging (MRI) study reveals large areas of restricted diffusion involving both cerebral hemispheres and distributed most notably around watershed areas. Those findings correlate with a large subacute infarction. The T2-weighted image at the same level shows a high-intensity signal. A thin subdural hemorrhage is observed in the posterior fossa on the right, on the tentorium, and along the transverse sinus. The susceptibility weighted image reveals additional foci of a subacute hemorrhage along the falx cerebri and both sides of the tentoria (Fig 3).

At that point, an unexpected anamnestic detail is provided by the infant's maternal grandmother. She comments to us that her daughter, who was also born in our hospital, had suffered from seizures that appeared on her third day after birth, and that they had been accompanied by a rash. Our patient's mother had



Figure 1. Nonspecific erythematous rash on lower limbs and lower abdomen at presentation.

been hospitalized in our NICU for 1 month. The sole abnormal laboratory finding was eosinophilia in serial blood cell counts. Findings on electroencephalography and brain computed tomography were normal. A current physical



Figure 2. Small area of alopecia on the right parietal side of the head at presentation.

examination of the mother reveals whorled hypopigmented areas along her lower limbs (Fig 4).

After excluding common causes of neonatal seizures, the unique clinical picture of general seizures and skin manifestations in a female infant whose mother had a similar course during her own neonatal period and childhood leads us to the presumptive diagnosis of incontinentia pigmenti (IP). A blood sample is sent for genetic analysis, and a large deletion of 11.7 kB of the *IKBKG* gene, encompassing exons 4 to 10, is detected. This deletion has been previously described as the cause of familial IP by Smahi et al. (1) To confirm inheritance, a genetic test of the mother is ordered and she is found to have the same mutation as her daughter. Because the maternal grandmother and her other daughter have no history of skin manifestation or any other symptoms that might correlate with IP, we assume that the mother of our patient had a de novo mutation.

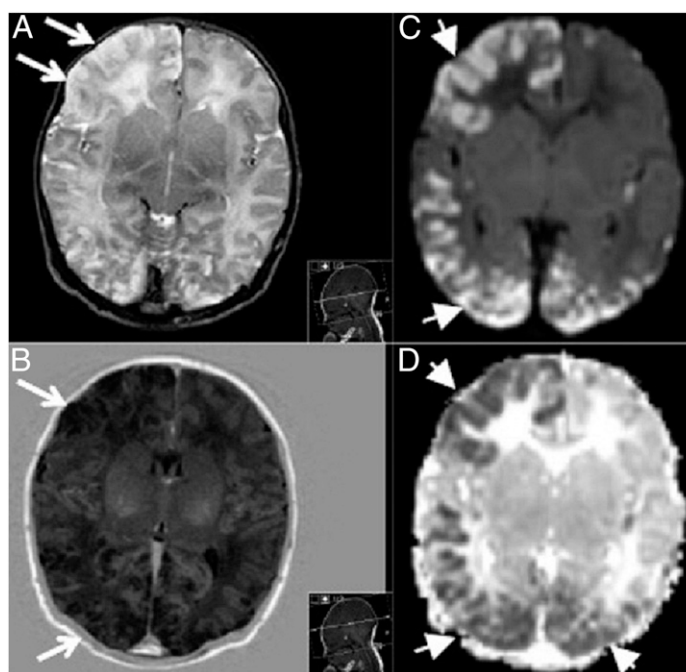
DISCUSSION

Neonatal seizures are associated with various medical conditions related to events that happen before, during, and after delivery. The differential diagnosis is broad, with the most common cause of neonatal seizures being perinatal asphyxia. (2) The presentation might be acute or chronic, and the condition might have modifiable or nonmodifiable etiologies that include infection, hematologic abnormalities leading to neonatal stroke, metabolic derangement, congenital malformations, and others.

IP is a rare X-linked dominant neurocutaneous disorder with not only pathognomonic skin findings but also a wide variety of nondermal manifestations. The disease was first described in 1906 by Garrod who reported a 2½-year-old girl with peculiar pigmentation of the skin and severe neurodevelopmental manifestations. (3) The term *incontinentia pigmenti* describes the histologic feature of a basal layer of the epidermis ("incontinent of melanin") and it was introduced in 1926 by Bloch. Sulzberger described non-dermatologic manifestations in the same child 2 years later, and the condition became known as *Bloch-Sulzberger syndrome*. (4)

The heritability of IP was noted by several investigators, among them Spallone, (5) who describe familial cases and note the affected female gender survivability along with male gender lethality. Parrish et al (6) reviewed the origins of new mutations in the *IP2* gene and described 15 cases in which more than one-half of the new mutations were paternal in origin. Interestingly, most of the clinical findings in IP develop and are manifested during the neonatal, infantile, and childhood periods, representing an ongoing

Figure 3. Magnetic resonance imaging studies. A. T2 image showing high intensity of the cortex in affected areas (arrows). B. T1 infrared image showing low intensity of the cortex in affected areas (arrows). C. and D. Diffusion weighted imaging and apparent diffusion coefficient map showing restricted diffusion of the cerebral cortex in affected areas (arrowheads).



inflammatory process that appears and fades with time (Fig 4). Late reactivation of the skin manifestations described in 2003 by Bodak et al (7) suggests the persistence of a mutant *NEMO* gene in the affected keratinocytes.



Figure 4. Skin manifestations of incontinentia pigmenti of the infant's mother. Stage 4 cutaneous manifestations are represented by scarlike lesions appearing as pale, hairless patches or streaks. These lesions developed during adolescence and persisted into adulthood.

Ocular findings are quite frequent in patients with IP, (1) ranging from mild changes in the retinal vasculature to complete retinal detachment. Our patient also has diffused retinal hemorrhages, but we consider them as being consistent with postdelivery status.

As a consequence of the rarity of the disease and its variable clinical picture, there are only a few descriptions of neuroimaging features characteristic of IP. Advanced neuroimaging studies, such as MRI, can reveal a chronic brain injury representing an intrauterine process, together with acute injuries that happen closer to the time of delivery. (8) The newborn in our case had subacute extensive cortical lesions together with acutely formed hemorrhages. Because she had been born with skin manifestations, one can assume that both the cerebral inflammatory process and the skin changes characteristic of IP took place during the same intrauterine period. Moreover, given that she had developed normally and was born at the 50th percentile for height and weight, it is reasonable to assume that the onset of brain injury was during the third trimester.

Lessons for the Clinician

- In an era of innovative medical technologies, anamnestic details and history taking remain the key elements for correct diagnosis.
- Genetic tests are today's "time tunnel" for revealing the true, untold, and sometimes unknown story of the infant, facilitating a healthier future for our offspring.

ACKNOWLEDGMENT

All authors have made substantive contributions to the case, and all authors endorse the data and conclusions.

American Board of Pediatrics Neonatal—Perinatal Content Specifications

- Know the differential diagnosis and syndromes associated with hyperpigmented lesions, including cafe au lait spots, giant hairy nevus, incontinentia pigmenti, and pigmented nevi.
- Understand the differential diagnosis and evaluation of neonatal seizures.

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Case 1: Seizures and Rashes Do Run in the Family

Amit Hochberg, Sylvia Foldi, Erez Nadir, Roni Shreter, Muhammad Mahajnah and
Michael Feldman

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Index of Suspicion in the Nursery

3 Seizures in a 2-day-old Infant

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AUTHOR DISCLOSURE Drs Baker and Yeganeh have disclosed no financial relationships relevant to this article. Dr Rao has disclosed she is on the speaker bureau for LivaNova, Inc. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 48-hour-old male infant born at 38+3/7 weeks' gestation is transported from home via ambulance to the emergency department (ED) for poor feeding, lethargy, duskiness, and rhythmic twitching of lower extremities. The mother received prenatal care from a midwife. The pregnancy was complicated by a maternal genital herpes outbreak in the first trimester. The mother was given valacyclovir for viral suppression and no herpetic lesions are noted at delivery. Clear artificial rupture of membranes is performed by the midwife 5 hours before delivery and the infant is born via vaginal delivery into a water birthing tub with a disposable liner. Apgar scores are 7, 8, and 9 at 1, 5, and 10 minutes. The umbilical cord is not cut based on the parents' request for umbilical nonseverance. The placenta is washed and dried, wrapped in muslin, and left attached to the infant until the midwife cuts the cord with sterilized scissors before transfer to the ED.

Postnatal history is remarkable for poor feeding. The infant has difficulty latching on and receives supplemental formula as well as donor unpasteurized breast milk from a lactation consultant. On the morning of admission, the infant has perioral cyanosis and is unresponsive.

In the ED, he is cyanotic with shallow respirations and is found to be hypothermic (rectal temperature of 95.3°F [35.2°C]), and hypoglycemic (peripheral blood glucose level of 15 mg/dL [0.83 mmol/L]) with multifocal clonic seizures. He is tachycardic, with a heart rate up to 180 beats/min, and his oxygen saturation is 85%. Dried umbilical stump is in place without any surrounding erythema. He is resuscitated, intubated for airway protection, and given a loading dose of levetiracetam.

DISCUSSION

Diagnosis and Hospital Course

Laboratory findings are notable for leukopenia with predominance of immature cells (immature to total neutrophil ratio 0.36), polycythemia, and thrombocytopenia. Cerebrospinal fluid (CSF) 60 hours after birth shows 2 white blood cells per microliter with normal glucose and protein.

Blood, urine, and CSF cultures are performed and the infant starts treatment with ampicillin, gentamicin, and acyclovir. Blood cultures from 2 separate peripheral draws are positive for *Staphylococcus epidermidis* sensitive to oxacillin (mean inhibitory concentration [MIC] ≤0.25). Urine culture performed via urethral catheterization shows less than 10,000 colony-forming units per

milliliter of *Escherichia coli*, susceptible to ampicillin (MIC ≤ 2). CSF bacterial culture remains negative. Polymerase chain reaction testing for herpes simplex virus (HSV) types 1 and 2 is negative in the specimens of blood and surface sites (conjunctivae, mouth, nasopharynx, and rectum) collected on admission and from CSF collected 8 days after birth. He completes a 2-week cefazolin course for both *S epidermidis* and *Escherichia coli*, and a 3-week acyclovir course for the possibility of HSV meningitis.

The placental microbiology culture is positive for *S epidermidis* with the same susceptibility pattern as the isolate from the infant's blood culture. Placental pathology does not show evidence of chorioamnionitis.

Magnetic resonance imaging shows T2 hyperintensity involving the occipital and parietal lobes, most prominently along the occipital gyri and along the calcarine fissures, consistent with hypoglycemia. In addition, foci of periventricular restricted diffusion are seen lining the margin of the posterior temporal horns, atria, and posterior bodies of lateral ventricles, as well as in the thalamus and basal ganglia, concerning for a central pattern of hypoxic-ischemic injury. Continuous electroencephalographic monitoring shows excessive discontinuity and excessive sharps, signs of cortical irritability, but no further seizure activity.

The patient completes his antibiotic course without any further seizure activity or hypoglycemic episodes. His endocrine metabolic workup is negative for other causes of hypoglycemia, and his presentation is suggestive of sepsis that resolved shortly after appropriate therapy.

We hypothesize that this infant developed *S epidermidis* sepsis secondary to colonization of the attached placenta soon after birth, which was transmitted through the attached umbilical cord. Sepsis then led to poor feeding, hypoglycemia, and hypothermia. The infant's presentation with seizures was secondary to the hypoglycemic encephalopathy, with a component of hypoxic-ischemic encephalopathy secondary to respiratory depression. Hypoglycemic encephalopathy of this severity usually leads to ulegyria, which can then contribute to the development of focal epilepsy later in infancy or childhood. In addition, the injury to the basal ganglia and subcortical structures could have potential impact on motor development.

The Condition

Neonatal Early-Onset Sepsis with *S epidermidis*. Most cases of early-onset sepsis (EOS) present in the first 24 to 48 hours after birth as the bacteria (most commonly group B *Streptococcus* and *E coli*) are transmitted before delivery

from contaminated amniotic fluid or during delivery from the mother's vaginal tract. (1)(2) The patient in the current case presented with sepsis later, which supports the hypothesis that the infection likely occurred shortly after birth. *S epidermidis* is a rare cause of EOS in term infants. (3) This patient had 2 positive blood cultures, with a time to positivity of less than 24 hours. In contrast to the paucity of this infection in term infants, *S epidermidis* sepsis is commonly encountered as a nosocomial infection in very low-birthweight infants in the NICU, particularly those with indwelling catheters. (3)

Umbilical Nonseverance ("Lotus Birth"). The term lotus birth is used when the placenta appears like a lotus flower attached to the infant via its long stem, and was first popularized by Claire Lotus Day in the early 1970s in the United States. (4) The placenta is often decorated or wrapped in a cloth and is kept close to the infant via the umbilical cord, which is allowed to dry and detach on its own, typically between 3 to 10 days after birth (Fig). This practice appears to be growing in popularity in the United States, United Kingdom, and Australia. Qualitative research suggests that some mothers perceive a spiritual connection between the placenta and the infant, and feel that it is the infant's choice to detach from the



Figure. Artist rendition of umbilical nonseverance ("lotus birth") with newborn attached to placenta until umbilical cord detaches on its own.

placenta as part of his or her transition. Others postulate that keeping the placenta attached may have some nutritional benefit with increased transfer of blood to the infant. (4)(5) This practice is not without risk. The Royal College of Obstetricians and Gynaecologists issued a statement regarding the lack of medical evidence around the benefits or safety of this practice. Because the placenta is blood-filled, it can become a highly effective culture medium for bacteria once it loses circulation and begins decomposing. Bacteria can then traverse the umbilical cord that remains attached to the infant, leading to EOS. (6)

Lessons for the Clinician

- Umbilical nonseverance or “lotus birth” is a risk factor for neonatal sepsis.
- *Staphylococcus epidermidis* is a rare cause of neonatal early-onset sepsis in term infants.
- Practices involving the placenta are growing in popularity and their health ramifications should be studied. Placental nonseverance can place the infant at risk for neonatal sepsis.

ACKNOWLEDGMENT

Shirin Towfiq contributed the artwork.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations and diagnostic features of neonatal infections with *Staphylococcus aureus* and *Staphylococcus epidermidis*.

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Case 3: Seizures in a 2-day-old Infant
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Case 3: Seizures in a 2-day-old Infant

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2 Seizures, Apnea, Lethargy, and Persistent Hiccups in a Full-Term Newborn

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PRESENTATION

A female infant weighing 3,265 g is born to a 34-year-old gravida 10, para 8 mother, at 39 5/7 weeks of gestation. The pregnancy is complicated by maternal drug use (cocaine and tetrahydrocannabinol) and inadequately treated group B *Streptococcus* colonization. The infant is delivered via a precipitous vaginal delivery with concerns for placental abruption because of the removal of several large blood clots. At delivery, meconium staining of fluids is noted but the infant is vigorous, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively.

At 14 hours after birth, the infant is first noted to have an episode of right upper extremity twitching, which soon progresses to involve both upper extremities. She also appears hypotonic and lethargic, and is noted to have episodes of apnea, bradycardia, and desaturations requiring continuous positive airway pressure. The infant undergoes a thorough screening for infections and is started on empirical broad-spectrum antibiotics and antiviral coverage (*Herpes simplex*). Serum glucose and electrolyte levels are normal. The infant is then transferred to a tertiary care facility for further care.

On arrival, the infant is noted to be lethargic and hypotonic with shallow breathing. She is also noted to have frequent hiccups. Capillary blood gas is notable for a pH of 7.29, a P_{aCO_2} of 64 mm Hg (8.5 kPa), and a base deficit of +4. The infant undergoes elective intubation and mechanical ventilation is started. A head computed tomography (CT) scan is obtained and the infant is placed on continuous electroencephalography (EEG) monitoring.

DISCUSSION

The head CT scan shows slightly diminished gray and white matter differentiation, but is otherwise unremarkable. Because of the infant's clinical presentation, serum ammonia, lactate, pyruvate, uric acid, urine organic acids, serum amino acids, urine reducing substances, and liver and renal function are also tested for metabolic disorders. EEG shows burst suppression pattern with multiple seizures characterized by 1- to 2-Hz poly-spike/sharp waves. The infant is given a loading dose of phenobarbital. Because of persistent seizure activity, she is given another dose of phenobarbital and started on pyridoxine and folinic acid. By day 4, the seizures are well controlled but the infant is noted to have increasingly frequent hiccups with persistent apnea requiring mechanical ventilation. The infant's evaluation for infections is unremarkable. Lumbar puncture (LP) is repeated and cerebrospinal fluid (CSF) is sent for levels of lactate, pyruvate, amino acids, and neurotransmitters along with concomitant repeat serum amino

AUTHOR DISCLOSURE Drs Arya and Melton have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

acids. Magnetic resonance imaging (MRI) of the brain with spectroscopy is also performed.

Differential Diagnosis

The initial presentation of the infant with lethargy, hypotonia, and seizures was concerning for sepsis. But the infant's evaluation for infections was negative. The perinatal history of maternal cocaine use, concern for placental abruption, and meconium staining at delivery also raised concerns for hypoxic-ischemic encephalopathy but the infant had normal examination findings for the first 14 hours after birth and an unremarkable resuscitation. Neonatal drug withdrawal was also a possibility, but the infant did not display any of the other associated symptoms.

A normal CT scan ruled out major structural anomalies and intracranial bleeding, and the MRI did not show signs concerning for a perinatal stroke. Urea cycle defects, organic acidemias, and fatty acid oxidation defects were ruled out because of normal serum glucose, ammonia, lactate and pyruvate, and urine organic acids. Given the persistent apnea and hypotonia, a diagnosis of nonketotic hyperglycinemia (NKH) was suspected.

The Condition

The MRI revealed symmetric diffusion restriction in the bilateral white matter, internal capsule, brain stem, and cerebellum, raising concerns for an inborn error of metabolism. Magnetic resonance spectroscopy revealed a glycine peak, which was suggestive of NKH. The serum amino acid testing revealed a glycine level of 12.8 mg/dL (1,709 $\mu\text{mol/L}$; normal 1.2–5.9 mg/dL [164–791 $\mu\text{mol/L}$]), the CSF glycine level was 3.1 mg/dL (418 $\mu\text{mol/L}$; normal <0.05 mg/dL [<7 $\mu\text{mol/L}$]), and CSF–serum glycine ratio was 0.24, which confirmed the diagnosis of NKH.

NKH, also known as *glycine encephalopathy*, is an autosomal recessive inborn error of glycine metabolism. (1) It is caused by defects in the glycine cleavage system (GCS) which is formed by 4 proteins P, H, T, and L encoded by the *GLDC*, *GCSH*, *AMT*, and *GCSL* genes, respectively. (2) This defect leads to an accumulation of glycine in different body compartments, including the CSF. (3) Glycine serves as both an inhibitory and excitatory neurotransmitter. Its

inhibitory activity in the brainstem and spinal cord is associated with apnea and hiccups, while its excitatory activity at the N-methyl-D-aspartate (NMDA) receptors in the cortex is associated with seizures. (4)

There are 2 types of NKH based on the timing of presentation: classic or neonatal, and atypical. In the classic form, neonates appear normal at birth but progress rapidly within the first few days to lethargy, hypotonia, apnea, and seizures. Persistent hiccups also are usually seen at presentation. (5) After the initial period of ventilator dependency, apnea resolves for most patients in 1 to 3 weeks. (6) Following the neonatal period, severe psychomotor disability is seen in most cases of classic NKH. (5) Congenital brain anomalies like hydrocephalus, retrocerebellar cyst, and abnormalities of the corpus callosum also have been reported with NKH, and their presence confers a poorer prognosis. (7)(8)

Infants with atypical NKH usually have normal development until 6 months of age and then present with 1) mental retardation and seizures (infantile form); 2) episodes of chorea, delirium, and vertical gaze palsies during febrile illnesses (episodic form); and 3) normal intellectual function with spastic diplegia, optic atrophy, and chorioathetosis (late-onset form). (5)(9)

Diagnosis of NKH is made by detecting hyperglycinemia and an elevated glycine level in the CSF with a CSF–plasma glycine ratio typically greater than 0.08. (1) This requires special attention to avoid a traumatic LP and CSF contamination with blood. Mass spectroscopy may also demonstrate a glycine peak, as seen in this case. The diagnosis can also be confirmed by detecting enzyme deficiencies by evaluating the GCS through a liver biopsy or in cultures of lymphoblasts. (10) It is also important to note that organic acidurias and ketoacidosis must be excluded, because inhibition of the GCS in the liver by organic acids can lead to ketotic hyperglycinemia but the CSF–plasma glycine ratio is usually normal. (1) Sodium valproate has also been shown to cause hyperglycinemia by inhibiting the GCS. (11)

Treatment

Existing therapies decrease seizure frequency and apnea and improve alertness; however, most patients with NKH progress to severe intellectual disability and the overall prognosis

TABLE. Weekly Plasma Glycine Monitoring Results

	NORMAL RANGE	DAY 3	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
Serum glycine	1.2–5.9 mg/dL (164–791 $\mu\text{mol/L}$)	12.8 mg/dL (1,709 $\mu\text{mol/L}$)	4.7 mg/dL (627 $\mu\text{mol/L}$)	1.8 mg/dL (249 $\mu\text{mol/L}$)	3.7 mg/dL (506 $\mu\text{mol/L}$)	4.9 mg/dL (653 $\mu\text{mol/L}$)	5.6 mg/dL (756 $\mu\text{mol/L}$)

remains poor, despite therapy. (12) Sodium benzoate undergoes conjugation with glycine to form hippurate, which is readily excreted by the kidneys. (13) It can reduce plasma glycine levels to normal but CSF glycine, although reduced, does not return to normal. (12) Dextromethorphan is a noncompetitive NMDA receptor antagonist.

Progression

Following a multispecialty care conference, the parents in the current case chose to initiate sodium benzoate and dextromethorphan treatment. In the next few days, the infant started showing increasing spontaneous movements and signs of spontaneous breathing, prompting extubation to room air. The infant also started taking partial-volume oral feeds. Plasma glycine levels were repeated weekly and showed an initial downward trend after beginning therapy, but levels started increasing again before discharge (Table). A glycine encephalopathy sequencing panel revealed that the patient was heterozygous for 3 notable missense variants in the *GLDC* gene.

Lesson for the Clinician

This case shows the importance of suspecting inborn errors of metabolism like NKH for an infant presenting with seizures, apnea, and persistent hiccups.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids.

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Case 2: Seizures, Apnea, Lethargy, and Persistent Hiccups in a Full-Term Newborn

Shreyas Arya and Kristin Melton

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Case 2: Seizures, Apnea, Lethargy, and Persistent Hiccups in a Full-Term Newborn

Shreyas Arya and Kristin Melton
NeoReviews 2019;20:e295
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Index of Suspicion in the Nursery

3 Severe Anemia in a Term Newborn

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PRESENTATION

A term 2,935-g appropriate for gestational age boy is born to a 22-year-old gravida 2, para 1001 woman at 38 and 1/7 weeks' gestation via an induced vaginal delivery. She received regular prenatal care and is followed closely during her pregnancy for maternal isoimmunization. The mother's laboratory tests reveal a blood type of AB, Rh negative, human immunodeficiency virus types I and II nonreactive, hepatitis B antigen nonreactive, rapid plasma reagin negative, and rubella immune. Her antibody screen is positive for warm autoantibodies to G and C with a combined titer of 1:64. Prenatal ultrasonography at 20 weeks notes a left atrophic multicystic kidney, a normal right kidney, and no other congenital anomalies. The mother is monitored with serial ultrasonography, revealing a stable, normal-range middle cerebral artery Doppler until 32 weeks' gestation. Her 32-week ultrasonography demonstrates a middle cerebral artery of 1.9 multiples of median. Amniocentesis yields a bilirubin level of 0.022 OD 450 nm, corresponding to zone 1 on the Liley curve, indicating mild or no disease. At 38 and 1/7 weeks the mother is noted to have a nonreactive nonstress test. Delivery is induced, and she proceeds to have an uncomplicated vaginal delivery.

After delivery, delayed cord clamping is performed for 45 seconds. The infant has a weak cry, but with adequate respiratory effort. A saturation probe is placed, revealing oxygen saturation of 52%. A 3/6 holosystolic murmur, mild to moderate retractions, and pallor are noted on examination. He is given blow-by oxygen at 100% fraction of inspired oxygen, which increases his oxygen saturation to 80%. The infant remains pale throughout the resuscitation and is transferred to the NICU.

PROGRESSION

A complete blood cell count is notable for a hematocrit value of 19%, normal red blood cell indices, and normal peripheral smear. Other laboratory values include a total bilirubin level of 2.8 mg/dL (47.88 μ mol/L), an absolute reticulocyte count percentage of 1.3%, direct antibody test positive, and antibody screen positive for C antibody. Results of a maternal Kleihauer-Betke test are negative. The infant is started on fluids and given 5 mL/kg packed red blood cell transfusion over 4 hours. His hospital stay includes 2 days of phototherapy for an elevated bilirubin level. He is confirmed to have a left atrophic multicystic kidney on postnatal ultrasonography and is referred to nephrology for follow-up. An echocardiogram shows a moderate atrial

AUTHOR DISCLOSURE Ms Do and Drs Motz and Parikh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

septal defect and a large patent ductus arteriosus, so cardiology follow-up is arranged. A thorough physical examination before discharge notes no syndromic features. His hematocrit value on discharge is noted to be 30%.

On follow-up in the hematology clinic at 10 days after birth he is noted to have a hematocrit level of 25% and is given a 10-mL/kg blood transfusion. At 2 months of age he is admitted for respiratory distress and pallor. At that time his hematocrit value was noted to be 5.3%. Further evaluation with a bone marrow biopsy reveals the diagnosis.

DISCUSSION

Diagnosis

On bone marrow biopsy, the patient was noted to have erythroid hypoplasia, with follow-up genetic studies revealing a pathogenic mutation at S ribosomal protein 24. A diagnosis of Diamond-Blackfan anemia (DBA) was made.

The differential diagnosis for neonatal anemia is broad but can be divided into blood loss, increased destruction, and decreased production. (1) The initial diagnosis for our patient's anemia seemed to be an obvious case of isoimmunization. The low reticulocyte count was puzzling, but in broadening the differential diagnosis we noted that our patient did not yet meet the diagnostic criteria for DBA. Nonetheless, we arranged follow-up with hematology for monitoring and further evaluation.

Diamond-Blackfan anemia is a congenital condition of bone marrow failure characterized by impaired erythropoiesis due to familial (autosomal dominant) or sporadic mutations affecting ribosome synthesis. (2) It is a rare disease with an annual incidence of 5 to 7 cases per million live births. Affected patients classically present within the first year after birth with a severe macrocytic anemia and reticulocytopenia that is often associated with congenital anomalies. Characteristic facial features have been reported; however, a wide range of congenital anomalies, such as ophthalmologic, cardiac, neck, thumb, and genitourinary, can also occur. (3)(4) An association with malignancy has also been suggested previously. (5)

Subsequent bone marrow biopsy reveals normal cellularity with paucity of erythroid precursors, and further genetic analysis reveals a characteristic mutation in S ribosomal proteins that causes failure of erythropoiesis. The

classic diagnosis of DBA is made when certain criteria are met: age younger than 1 year, isolated macrocytic anemia, reticulocytopenia, and normal marrow cellularity with paucity of erythroid precursors. A probable diagnosis is made if the previous criteria are not met but the patient has an associated gene mutation, a positive family history, or a combination of other minor laboratory anomalies. (1)(3)(4)(6)

Neonatal anemia due to decreased red blood cell production includes transient erythroblastopenia of childhood (TEC), Fanconi anemia, Schwachman-Diamond syndrome, and dyskeratosis. The latter 3 diagnoses are characterized as aplastic anemias that present with pancytopenia and hypocellular bone marrow, which help differentiate them from DBA. (2)(7)

TEC is a transient acquired condition of decreased red blood cell production of currently unknown etiology. Patients often have a preceding viral illness and a more moderate form of anemia. Other distinguishing features of TEC include presentation after a year of age, a normocytic anemia, and no congenital anomalies. (2)(8) These characteristics are distinct from DBA and aid in making the correct diagnosis. (9)

Treatment and Prognosis

Mainstays of treatment include corticosteroids and blood transfusions; hematopoietic stem cell transplant is an option for patients with corticosteroid-refractory disease. (5)

The body of research regarding the rare diagnosis of DBA continues to grow, with a focus on expanding the treatment options and elucidating the incidence of associated malignancy via the DBA Registry. (6)

Lessons for the Clinician

- The differential diagnosis for neonatal anemia is broad but can be divided into blood loss, increased destruction, and decreased production.
- Neonatal anemia can be due to multiple concurrent causes.
- Specialist follow-up for neonatal conditions is a necessary and critical component of an appropriate NICU discharge.
- Diamond-Blackfan anemia is a congenital condition of bone marrow failure characterized by impaired erythropoiesis due to familial (autosomal dominant) or sporadic mutations affecting ribosome synthesis.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology and pathophysiology of hemolytic anemia in the neonate.
- Know the clinical and laboratory features of hemolytic anemia in the neonate.
- Know the causes of and diagnostic approach to an infant who is anemic at birth.
- Know the clinical indications for use of blood products in neonates, as well as the manifestations and prevention of potential complications of transfusion.

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Case 3: Severe Anemia in a Term Newborn

Julie Do, Patrick Motz and Pratik Parikh

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Case 3: Severe Anemia in a Term Newborn

Julie Do, Patrick Motz and Pratik Parikh

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Index of Suspicion in the Nursery

2 Severe Hyperammonemia in a Neonate: An Alternate Ending

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PRESENTATION

A male infant is born at 38 weeks 3 days of gestational age to a gravida 5, para 1 woman via spontaneous vaginal delivery, after a pregnancy complicated by maternal preeclampsia. Maternal history is significant for 2 early miscarriages and an ectopic pregnancy. All prenatal laboratory findings, including maternal immunoglobulin G for herpes simplex virus (HSV), had been normal or negative. The family history is unremarkable. The infant requires normal newborn care and is discharged from the hospital on day 2 after birth. His parents note that he had been sleepy and a poor feeder. He is hypothermic and tachypneic at his first newborn visit to the pediatrician and is immediately referred to the emergency department.

Septic evaluation reveals HSV in both serum and cerebrospinal fluid. Ammonia concentration is normal and his complete blood cell count reveals leukopenia. Initial treatment includes acyclovir, cefotaxime, and ampicillin, narrowed within 48 hours to acyclovir monotherapy. His condition rapidly declines and he develops respiratory failure on hospital day (HOD) 1. The ammonia concentration is within the normal range (39 $\mu\text{g/dL}$ [28 $\mu\text{mol/L}$]). Feeding is initiated on HOD 2 with a subsequent rise in the ammonia concentration (113 $\mu\text{g/dL}$ [81 $\mu\text{mol/L}$]). Despite the cessation of feeding and initiation of moderate glucose infusion rate, the ammonia concentration rises to 538 $\mu\text{g/dL}$ (384 $\mu\text{mol/L}$) by HOD 4. The patient is transferred to a different hospital for metabolic consultation.

DISCUSSION

Increased glucose infusion rate along with a bolus of sodium benzoate and sodium phenylacetate did not sufficiently improve this infant's hyperammonemia. Continuous renal replacement therapy (CRRT) was initiated when the ammonia concentration exceeded 700 $\mu\text{g/dL}$ (500 $\mu\text{mol/L}$). The highest measured ammonia concentration was greater than 1,400 $\mu\text{g/dL}$ (1,000 $\mu\text{mol/L}$). The patient's hyperammonemia initially improved with CRRT but quickly rebounded after stopping therapy, requiring further CRRT. CRRT was gradually weaned, and protein supplementation was slowly introduced through total parenteral nutrition, and the patient had no additional issues with hyperammonemia.

AUTHOR DISCLOSURE Drs Sheppard, Herrick, Cohen, and Flibbotte have disclosed no financial relationships relevant to this article. Dr Ahrens-Nicklas has disclosed that she is supported by NIH grant 2T32GM008638-21. Dr Pyle has disclosed that she is supported by NIH grant KL2TR001879-02. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

In this case, a history of poor feeding, sleepiness, hyperammonemia developing after feeding, hyperammonemia out of proportion with liver dysfunction, and the degree of elevated ammonia concentration raised suspicion for proximal urea cycle defects. Not all proximal urea cycle defects are included on US newborn screening, and can be missed. The ultimate resolution of the hyperammonemia, even after initiation of protein-based feeds, made these diagnoses unlikely. Initial liver function tests, coagulation studies, newborn screening, and abdominal ultrasonography were normal. The patient had no lacticemia, hypoglycemia, ketonuria, or acidosis. Initial acylcarnitine profile, plasma amino acids, urine orotic acid, and urine organic acids, all measured before the infusion of sodium benzoate and sodium phenylacetate, resulted in no diagnostic pattern. Given the severity of the child's condition, rapid whole exome sequencing was performed and was also negative. Ultimately, the hyperammonemia was attributed to disseminated HSV infection, including severe HSV pneumonitis, similar to a previously reported case. (1)

This infant's hospital course was complicated by severe respiratory failure and acute respiratory distress syndrome necessitating high-frequency oscillator ventilation. He also suffered bilateral pneumothoraces requiring the placement of multiple chest tubes. Due to refractory air leak, despite maximal medical management including chest tubes, paralysis, and high frequency jet ventilation, the patient was placed on venoarterial extracorporeal membrane oxygenation (ECMO). Pneumothoraces resolved, and after 13 days, the patient underwent successful decannulation. He was weaned off respiratory support, and transitioned from parenteral to enteral nutrition. After ECMO, magnetic resonance imaging showed normal brain parenchyma with a small focus of extra-axial blood products over the left frontal lobe. The infant was discharged from the hospital. On follow-up at 9 months of age, the infant was feeding orally and growing well. ECMO was not available for the previously reported case, which was fatal. (1)

Ammonia is a byproduct of protein metabolism that, when elevated, can present with signs and symptoms of neurotoxicity. In a neonate, these include poor feeding, vomiting, lethargy, seizures, and encephalopathy and can mimic sepsis. (2)(3) Hyperammonemia may be precipitated by illness, such as sepsis, prematurity, liver immaturity, or inborn error of metabolism. Inborn errors of metabolism include primary urea cycle defect or secondary hyperammonemia in organic acidurias, mitochondrial disease, or substrate deficiencies. (2) Hyperammonemia is diagnosed

using a free-flowing blood sample placed on ice. (4) The underlying cause for the hyperammonemia should be determined simultaneously with treatments aimed at lowering the ammonia level in the patient. Laboratory evaluation should include plasma glucose, complete metabolic panel, coagulation factors, plasma acylcarnitines, plasma amino acids, urine organic acids, and urine orotic acid. (4) An evaluation for infection and liver imaging may also be clinically indicated.

Regardless of the origin, prompt management of hyperammonemia in the newborn is important for neurodevelopmental outcomes. (5)(6) Early in a disease process, the different etiologic factors may be indistinguishable. (2) Initial medical management includes decreasing ammonia production and increasing ammonia removal. (4) Preventing catabolism with high-dextrose intravenous fluids with a target glucose infusion rate of 8 to 10 mg/kg per minute and limiting protein intake may help to decrease the production of ammonia. Protein intake should be restricted for more than 24 to 48 hours because excessive protein restriction may lead to catabolism of endogenous protein. Nitrogen scavengers, such as sodium phenylbutyrate and sodium benzoate, will aid in the removal of ammonia. Amino acid supplementation may be helpful in primary urea cycle defects. The usefulness of dialysis in the treatment of hyperammonemia has been studied in patients with inborn errors of metabolism and sepsis. (1)(6)(7)(8) Indications for dialysis include blood ammonia levels of 560 to 700 $\mu\text{g/dL}$ (400–500 $\mu\text{mol/L}$) in neonates and insufficient response to medical management, though others have used thresholds of 280 $\mu\text{g/dL}$ (200 $\mu\text{mol/L}$). (4)(9) In the management of hyperammonemia, it is extremely important to be cognizant of one's resources, because timely transfer of the neonate to a metabolic center or larger children's hospital with access to ammonia scavengers and dialysis may be necessary. Early consultation with a metabolic physician is recommended.

Lessons for the Clinician

- Always consider hyperammonemia in the evaluation for neonatal sepsis, especially in the setting of poor feeding, vomiting, lethargy, seizures, and encephalopathy.
- Early management of hyperammonemia is crucial for improved neurodevelopmental outcomes and transfer to a metabolic center or larger children's hospital may be necessary.
- Lung rest strategies via extracorporeal membrane oxygenation are a potential solution for refractory air leak in a neonate.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.
- Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants.
- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.

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Case 2: Severe Hyperammonemia in a Neonate: An Alternate Ending
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Index of Suspicion in the Nursery

1 Severe Jaundice in a 2-day-old Term Neonate

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PRESENTATION

A 2-day-old, 2.68-kg term male neonate is brought to the emergency department with lethargy, poor feeding, and significant generalized jaundice. He was born via spontaneous vaginal delivery at home to a gravida 4, para 3 Amish woman under the supervision of a midwife, at an estimated gestational age of 39 weeks after an uncomplicated pregnancy with scant prenatal care. Jaundice was noticed 7 hours after birth. The neonate has only breastfed 5 to 6 times since birth, and passed a normal-colored stool at home. Prenatal laboratory findings are unavailable because of limited prenatal care. The mother's blood type is AB, Rh negative. The mother's obstetric history includes a previous miscarriage (4 years earlier), a previous stillbirth at 30 weeks' gestation (3 years earlier), and a term pregnancy (2 years earlier). She had received Rh_o(D) immune globulin 3 weeks after the miscarriage, 2 weeks after the stillbirth delivery, and 2 weeks after the most recent pregnancy. The mother, father, and 2-year-old brother are reportedly healthy.

Review of systems at admission is significant for decreased activity, poor feeding, and generalized, intense yellow discoloration of the skin. The infant has no fever, vomiting, diarrhea, constipation, bloody stools, seizures, or hypertonia. Physical examination reveals a weak cry, lethargy, scleral icterus, soft liver edge 3 cm below the right costal margin, and significant generalized jaundice of the entire body. No dysmorphic features are appreciated.

CASE PROGRESSION

Initial evaluation revealed a total serum bilirubin (TB) of 49.4 mg/dL (845 μ mol/L), conjugated bilirubin of 42 mg/dL (718 μ mol/L), unconjugated bilirubin of 10.7 mg/dL (183 μ mol/L), reticulocyte count greater than 23, and hemoglobin of 12.6 g/dL (126 g/L). Urinalysis demonstrated dark brown urine. Serum aspartate aminotransferase (AST) was elevated at 239 U/L (4 μ kat/L), serum alanine aminotransferase (ALT) was elevated at 55 U/L (0.9 μ kat/L), serum alkaline phosphatase was 186 U/L (3.1 μ kat/L), and partial thromboplastin time was elevated at 30.7 seconds. Urine culture revealed *Escherichia coli* at 10,000 to 100,000 colony-forming units. Peripheral smear demonstrated mild anemia with marked reticulocytosis and numerous immature erythroids. The neonate's blood type was B, Rh positive. Direct Coombs test result was 4+, indicating antibody-mediated hemolysis in the newborn. A jaundice chip, which targets 5 genes (*ABCB11*, *ABCB4*, *ATP8B1*, *JAG1*, and *TJP2*), was drawn (the negative result was not received until later, ruling out Alagille syndrome and progressive familial intrahepatic cholestasis as possible causes). Endocrinopathies (hypothyroidism

NOTE The editors and staff of NeoReviews find themselves in the fortunate position of having too many submissions for the Index of Suspicion in the Nursery column. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will make an announcement in NeoReviews when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

AUTHOR DISCLOSURE Drs Lyle and Turcu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Turcu's current affiliation is Department of Pediatrics, Division of Newborn Medicine, Tufts Medical Center, Boston, MA.

and hypopituitarism) were excluded (normal thyroid-stimulating hormone and free thyroxine). Newborn screening results were normal. Abdominal ultrasonography showed a normal-appearing liver and gallbladder, no biliary ductal dilation, and patent vessels.

The 2004 American Academy of Pediatrics guidelines for treatment of hyperbilirubinemia state that, “In unusual situations in which the direct bilirubin level is 50% or more of the TB, there are no good data to provide guidance for therapy.”⁽¹⁾ Treatment included intensive phototherapy, intravenous fluids, double volume exchange transfusion, intravenous immunoglobulin, ampicillin, cefotaxime, acyclovir, and phenobarbital (for activation of the promoter sequence of hepatic UGT1A1). The Fig demonstrates the decline of bilirubin after each of these interventions. Enteral feeds were initiated after 2 days of hospitalization, which the infant tolerated well.

At discharge on hospital day 7, laboratory findings were as follows: TB 9.3 mg/dL (159 μ mol/L), conjugated bilirubin 4.5 mg/dL (77 μ mol/L), unconjugated bilirubin 2.5 mg/dL (42.8 μ mol/L), AST 81 U/L (1.3 μ kat/L), ALT 36 U/L (0.6 μ kat/L), and alkaline phosphatase 82 U/L (1.4 μ kat/L). Hepatobiliary iminodiacetic acid scan was offered, but the parents declined because of the normal hepatic ultrasound scan with decreasing bilirubin levels. They also declined brain magnetic resonance imaging because the neurologic findings at discharge were reassuring.

FOLLOW-UP

The infant was evaluated in the developmental pediatrics clinic at 2 months, 19 days of age. Growth was appropriate: weight 5.88 kg (36th percentile), length 59.7cm (35th percentile), and head circumference 38.5cm (9th percentile). Jaundice had resolved. TB concentration was 0.8 mg/dL (13.7 μ mol/L) and direct bilirubin 0.0 mg/dL (0.0 μ mol/L). He appeared developmentally appropriate with normal findings on neurologic examination. He continues to be followed closely.

DISCUSSION

Jaundice in the first few days after birth is a common neonatal problem, occurring in approximately two-thirds of newborns. (2) Most cases are represented by unconjugated hyperbilirubinemia, which is usually treated with phototherapy. Conjugated hyperbilirubinemia is much less common in the neonatal period, and is indicative of cholestasis. Neonatal jaundice caused by unconjugated versus conjugated hyperbilirubinemia cannot be differentiated with physical examination alone. Direct bilirubin concentration greater than 1.0 mg/dL (17.1 μ mol/L) with TB less than 5 mg/dL (85.5 μ mol/L), or a direct bilirubin greater than 20% of the TB (if TB >5 mg/dL) is diagnostic of conjugated hyperbilirubinemia. Conjugated hyperbilirubinemia and cholestasis can have infectious, metabolic, or

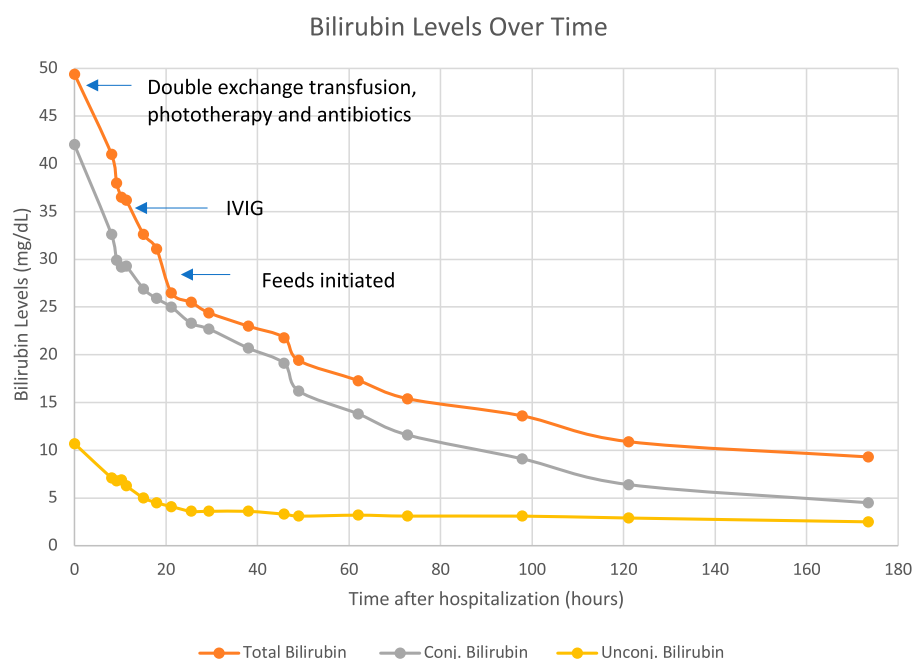


Figure. Bilirubin levels over time.

obstructive causes, and is the most common marker of cholestasis. (3)(4)(5)(6)(7) Common causes of obstructive cholestasis include biliary atresia, choledochal cysts, bile duct paucity, neonatal sclerosing cholangitis, inspissated bile syndrome, gallstones/biliary sludge, cystic fibrosis, and Caroli disease. (2)(7)(8)

The current patient was born full term, had inadequate prenatal care, and demonstrated significant generalized jaundice within the first 7 hours after birth. He presented with hemolytic anemia (likely because of Rh incompatibility) and conjugated hyperbilirubinemia (which was unusual given that Rh incompatibility usually results in unconjugated hyperbilirubinemia). The most common causes of cholestasis had been excluded: Alagille syndrome and progressive familial intrahepatic cholestasis (negative jaundice chip), hypothyroidism and hypopituitarism (normal thyroid-stimulating hormone and free thyroxine), congenital heart disease (normal chest radiograph and a patent foramen ovale on echocardiography). Urinary tract infection with *E coli* could have been a contributory factor, but it is an unlikely main cause. In cases of suspected cholestasis, ultrasonography is the initial imaging modality of choice. (9) After all test results returned, the exclusion diagnosis in this case remained Rh incompatibility with severe chronic hemolysis, complicated by inspissated bile syndrome.

Inspissated bile syndrome is a rare clinical entity, with an incidence of 1 in 175,000 live births as reported in England. (9)(10) The medical literature reveals a paucity of neonatal inspissated bile syndrome cases; the few cases reported are in the setting of cystic fibrosis or metabolic disorders, (6)(11) ABO incompatibility after transfusion, (12) or drug-induced. (13) In these cases, the infant was older at the time of presentation, and TB and conjugated bilirubin levels were well below the values recorded for our patient.

Lessons for the Clinician

- Two-thirds of newborns will experience jaundice within the first few days after birth.
- Conjugated hyperbilirubinemia is less common than unconjugated hyperbilirubinemia and is indicative of cholestasis caused by infection, metabolism defects, or obstruction.
- Common causes of obstructive cholestasis include biliary atresia, choledochal cysts, bile duct paucity, neonatal sclerosing cholangitis, inspissated bile syndrome, gallstones/biliary sludge, cystic fibrosis, and Caroli disease.
- Evaluation for neonatal cholestasis includes blood, urine, and cerebrospinal fluid cultures, urinalysis, cerebrospinal fluid studies, complete blood cell count with differential, comprehensive metabolic panel, prothrombin

time/international normalized ratio, and partial thromboplastin time. Newborn screening results should be reviewed for possible metabolic causes. Abdominal ultrasonography should be performed to assess for biliary atresia. A jaundice chip is useful if Alagille syndrome or progressive familial intrahepatic cholestasis is suspected.

Note: This case is based on a presentation by Drs Lyle and Turcu at the Joint Plenary Poster Session of the Southern Regional Meeting of American Federation for Medical Research, New Orleans, LA, on February 22, 2018 (Poster No. 303).

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the factors, including red cell life span, enzyme defects, and red cell structural abnormalities, associated with an increase in bilirubin production.
- Know the factors associated with a decrease in neonatal serum bilirubin excretion, including those that affect the enterohepatic circulation of bilirubin.
- Know bilirubin physiology, including pathways of synthesis, transport, and metabolism, in the fetus and neonate.

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Case 1: Severe Jaundice in a 2-day-old Term Neonate

Allison Lyle and Rodica Turcu

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Index of Suspicion in the Nursery

2 Severe Respiratory Distress at Birth: A Rare Cause

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Jayashree Mondkar, MD*

**Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, India*

PRESENTATION

A full-term female infant is born with a weight of 2,500 g to a gravida 4, para 2 woman. The mother had no antenatal risk factors and antenatal ultrasound scans are normal. The infant is delivered vaginally and cries immediately after birth. Within a few minutes of birth, she develops severe respiratory distress, and her oxygen saturation drops to 65% in room air. She undergoes intubation in the labor room and is moved to the NICU for mechanical ventilation. Arterial blood gas measurement shows respiratory acidosis, and the ventilator settings are at peak inspiratory pressure of 18 cm H₂O with a positive end-expiratory pressure of 6 cm H₂O and FiO₂ of 0.5 with Pco₂ of 68 mm Hg. Chest radiography shows a complete homogeneous opacity in the right hemithorax with dextrocardia (Fig 1).



Figure 1. Chest radiograph showing right-sided homogeneous opacity.

AUTHOR DISCLOSURE Drs Kalamdani, Manerkar, Bhisikar, and Mondkar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PROGRESSION

The infant receives mechanical ventilation for 4 days. Antibiotics are started in view of the homogeneous opacity on the chest radiograph. Septic screening result is negative and blood cultures also turn out negative. Serial chest radiography continues to show the homogeneous opacity in the right hemithorax. Two-dimensional echocardiography is performed in view of the dextrocardia, which reveals dextroposition of a structurally normal heart.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for a term infant with respiratory distress with persistent right hemithorax opacification includes:

1. Pneumonia—consolidation
2. Collapse of the right lung
3. Bronchopulmonary sequestration
4. Scimitar syndrome
5. Mucus plug in the right main bronchus
6. Pulmonary hypoplasia

ACTUAL DIAGNOSIS

The opacity in the right hemithorax persists and computed tomography (CT) of the chest is performed. It reveals

complete aplasia of the right lung with absence of right pulmonary artery (Fig 2). Rest of the abdomen and cardiac CT scan is normal. The infant is gradually weaned off mechanical ventilation to high-flow nasal therapy on day 5 after birth. She continues to receive high-flow therapy for 5 more days and then is weaned to room air. Feeds are introduced on day 3 after birth and she starts breastfeeding on day 10. She is discharged from the hospital on day 15 after birth.

DISCUSSION

Lung agenesis/aplasia is a rare congenital anomaly with most recent estimated incidence of 1.2 per 100,000 live births. (1) It is characterized by the absence of main bronchi, pulmonary vessels, and lung parenchyma. It may be an isolated finding or associated with other anomalies of other organ systems. Commonly associated anomalies include tracheoesophageal fistula, heterotaxy syndromes with cardiac malpositions, aortic stenosis, total/partial anomalous venous connections, and sometimes vertebral defects, *anal atresia*, cardiac defects, *tracheoesophageal fistula*, renal anomalies, and limb abnormalities (VACTERL) anomalies. However, our patient did not have any other congenital anomaly. (2)(3)(4)

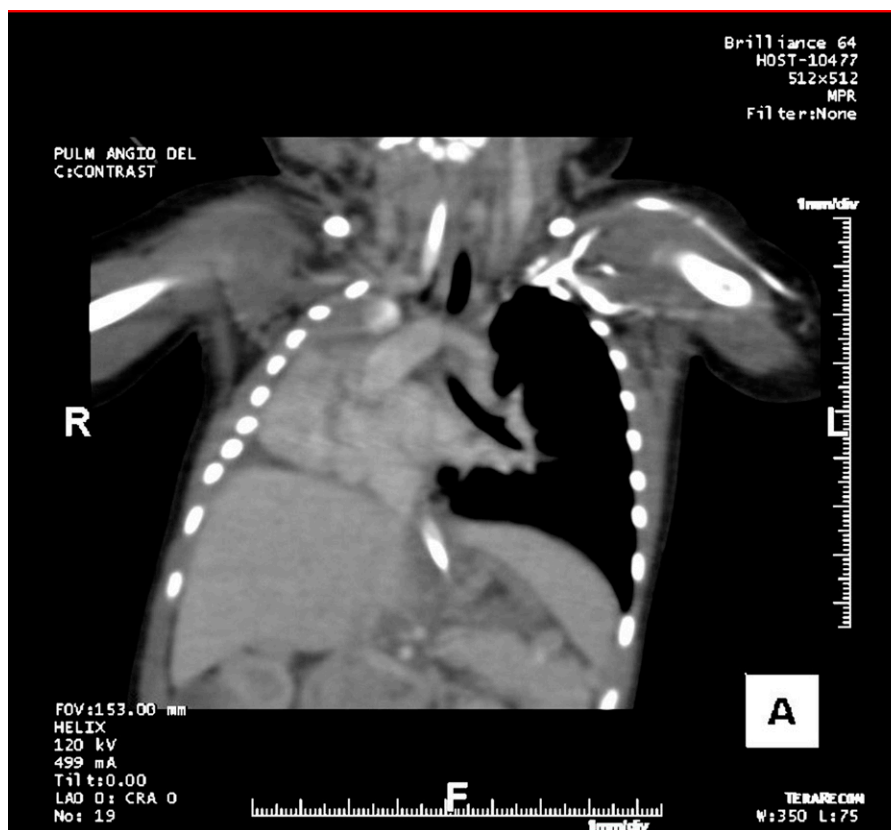


Figure 2. CT scan of the chest showing lung aplasia.

The condition can be diagnosed antenally using ultrasonography and fetal echocardiography. Recently a systematic approach has been developed in assessing lung agenesis, which is associated with cardiac anomalies. (5)

This condition may be asymptomatic at birth and may present in infancy and childhood as a case of respiratory distress or as frequent lower respiratory tract infections. Lung agenesis may present in the neonatal period as a case of respiratory distress or may progress to respiratory failure in severe cases. In our case, respiratory failure was impending in the labor room soon after birth, requiring ventilation. The diagnosis requires a high index of suspicion because the radiographic picture may closely resemble the more common diagnoses of pneumonia/consolidation; the diagnostic modality of choice is CT.

Management in the neonatal period is mostly about respiratory support. It can range from noninvasive respiratory support to invasive ventilation and high-frequency oscillatory ventilation. The degree of respiratory support required and the recovery depends on other associated anomalies and the pathology of the other lung.

The long-term outcomes of patients with lung agenesis are unclear, especially from low- and middle-income countries. The current patient is presently 8 months old without any respiratory morbidity and is developmentally normal.

Lessons for the Clinician

- Lung aplasia/agenesis is a rare congenital anomaly and can present with significant respiratory distress at birth or in the first few days after birth.
- Nonresolving pneumonia or a persistent radiographic image of pneumonia/collapsed lung should prompt further investigation for an anatomic abnormality.

- CT is the modality of choice for the diagnosis of this condition.
- With optimum ventilatory support, children with lung aplasia/agenesis recover and lead relatively healthy lives.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the stages and mediators of normal and abnormal cellular and structural development of all components of the lung.

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Case 2: Severe Respiratory Distress at Birth: A Rare Cause
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Index of Suspicion in the Nursery

2 Soft Tissue Congenital Neck Mass

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PRESENTATION

A female infant at 35 weeks and 4 days of gestation is born at a community hospital to a 25-year-old primigravida woman via emergency cesarean section because of fetal distress. Prenatal care had been good, and unexplained polyhydramnios had been noted during an otherwise uncomplicated pregnancy. The infant requires full cardiopulmonary resuscitation. Apgar scores are 0, 2, and 3 at 1, 5, and 10 minutes, respectively. At delivery, it is noted that she has a right neck mass, and she remains intubated for airway protection. The infant is transferred to another facility where she receives therapeutic hypothermia for 72 hours before being transferred to the tertiary care center for further evaluation of the mass and airway. On admission, she is noted to have superior vena cava syndrome with facial plethora. Radiography shows deviation of her airway to the left (Fig 1A). Computed tomography (CT) and magnetic resonance imaging (MRI) reveal a 5.2×3.6×2.4-cm multiloculated cystic, heterogeneous, septated mass with multiple fluid levels displacing mediastinal structures and compressing the right internal jugular vein, right internal carotid artery, right subclavian artery and vein, right vertebral artery, and the trachea (Fig 1B); it extends from the level of the inferior thyroid gland into the superior mediastinum.

The next day, day 6 after birth, an open excisional biopsy and fine needle aspiration is performed to evaluate for any pathology. Because of her worsening clinical status, the patient is taken to the operating room on day 10 after birth for excision of the mass. The mass is found to be adherent to the posterior mediastinum, extending through the chest into the neck, abutting and adherent to the trachea, extending over the anterior part of the esophagus, and adherent to the spine. No residual mass was left in the chest, but 2 areas of residual mass were left near the trachea and brachial plexus. The patient's superior vena cava syndrome improves dramatically and her clinical status stabilizes. Ten days later, she undergoes successful extubation. Micro-laryngoscopy and bronchoscopy confirm no airway narrowing at the time of extubation.

Pathology reveals fibrous histiocytic tumor, most likely juvenile xanthogranuloma (JXG). Pediatric oncology recommends chemotherapy with clofarabine, which is started in the NICU. She is transferred after 2 rounds of clofarabine to the oncology service. She undergoes plication of the right hemidiaphragm 2 months after extubation because of continued respiratory distress, likely secondary to diaphragmatic eventration; she is able to wean slightly on respiratory support, but remains hospitalized requiring high flow. One week later, radiography shows a stable opacity of unclear etiology (true soft tissue mass vs small-volume pleural fluid) in the region of the right upper lobe without mediastinal shift (Fig 2A). Two

AUTHOR DISCLOSURE Drs Patel, Mayfield, and Stefanescu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

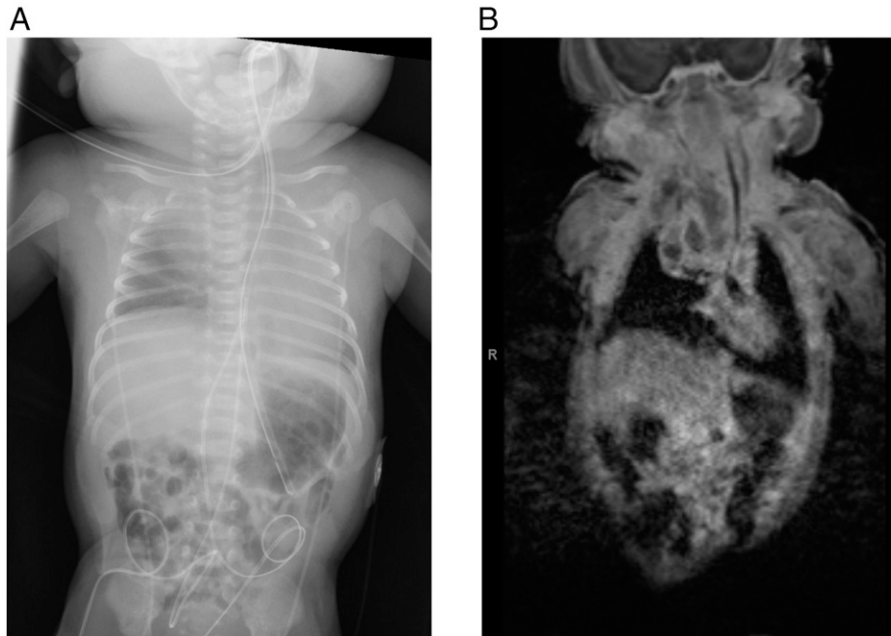


Figure 1. A. Radiograph showing deviation of the trachea and esophagus to the left. Soft tissue mass is also visible over the right upper lung fields. Right and left diaphragms are uneven. B. Coronal MRI showing a multiloculated cystic and septated mass with multiple fluid levels resulting in deviation of mediastinal structures.

weeks later, because of worsening respiratory distress, another radiograph is obtained, which reveals a right lung opacity with left shift of the mediastinum (Fig 2B). The patient had received her third round of clofarabine in the interim between Figs 2A and 2B. An urgent CT shows recurrence of the mass with extension into the spinal column and deviation of the spinal cord, trachea, and esophagus (Fig 3A-D). The mass measures $5.8 \times 4.8 \times 4.3$ cm in the cervical region, larger than the original mass. The patient is intubated and emergently transferred to another center with

pediatric neurosurgery. She subsequently dies during surgery because of hemorrhage.

DISCUSSION

JXG is a rare nonmalignant histiocytic tumor of dendritic cell origin with onset most often in infancy. Lesions may be present at birth. The incidence is estimated at 1 in 1 million children. (1) It is most often found as a solitary cutaneous skin nodule of the head and neck region, with other

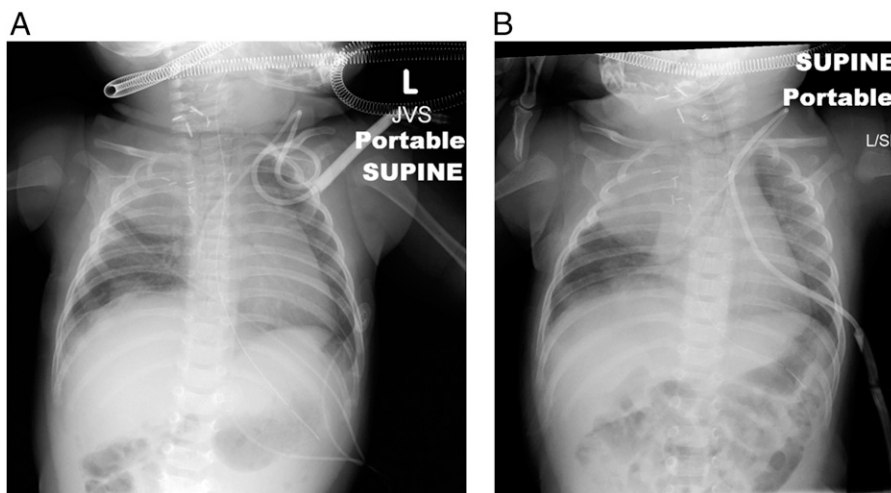


Figure 2. A. Radiograph after 2 courses of clofarabine shows a stable right upper lobe opacity of unclear etiology without mediastinal shift. B. Two weeks later, radiograph after a third course of clofarabine shows enlargement of the right upper lobe opacity with mediastinal shift.

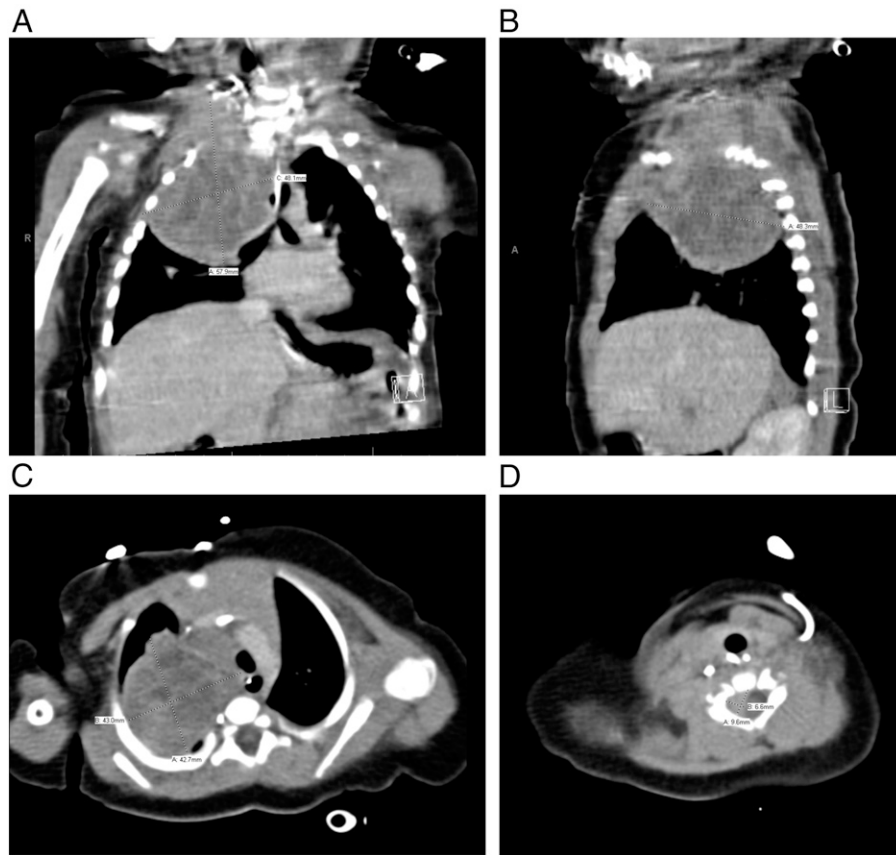


Figure 3. A. Coronal CT showing large heterogenous mass occupying the right upper thorax and extending into the neck. B. Sagittal CT showing the anterior-posterior dimension of the mass. C. Axial CT showing deviation of the mediastinal structures. D. Axial CT showing extension of the mass into the spinal column with deviation of the spinal cord.

common locations including the trunk and extremities. Other manifestations of JXG include systemic disease, solitary subcutaneous mass, multiple cutaneous lesions, and deep soft tissue mass. (2) The diagnosis of systemic disease requires the involvement of at least 2 visceral organs, with the central nervous system and liver being the most common sites. (3) JXG often regresses spontaneously within 1 year of presentation, and observation is the recommended treatment in most cases. If intervention is needed, the treatment is often steroids. However, when the mass causes clinical compromise, resection is recommended. After resection, even if residual tumor remains, JXG often regresses spontaneously. Chemotherapy is not recommended except in the case of nonresectable tumors in patients with clinical compromise, or in patients with systemic disease and vital organ involvement. Chemotherapy with Langerhans cell histiocytosis (LCH) treatment regimens, such as prednisone and vinblastine, or with medications such as clofarabine and cladribine, has been used. (1)(4)(5)

The differential for fibrohistiocytic tumors includes angiomatoid fibrous histiocytoma, LCH, and other non-LCH

tumors such as Erdheim-Chester disease and Rosai-Dorfman disease. (3) Immunohistochemistry is important in differentiating these tumors, but is not diagnostic. In JXG, mononuclear and spindle cells are often immunoreactive for CD68, CD14, CD163, and factor XIIIa, and nonreactive for CD1a and S100 protein. (1)(2)(3) For angiomatoid fibrous histiocytoma, cells are immunoreactive for vimentin, epithelial membrane antigen, desmin, and CD68 and negative for S100 protein. (6) For LCH, diagnosis is supported by the presence of S100 protein and CD1a, which helps distinguish LCH from JXG. (3) In the current patient, pathologic findings included immunoreactivity toward CD68, CD163, and factor XIIIa, and nonreactivity to CD1a, S100 protein, epithelial membrane antigen, and desmin, among a number of other factors, which is most consistent with JXG. Touton giant cells, which are usually present in the classic form of JXG, (1)(2)(3) were not noted in the current case.

This case is unique because the deep soft tissue JXG rapidly increased in size and invaded the spinal column, causing clinical compromise despite resection and ongoing

treatment with clofarabine. Barroca et al report a similar case of a cervical JXG that recurred after resection. (7) Histopathology was similar and Touton giant cells were not present. However, the recurrence was less severe and the patient was not receiving medication at the time of recurrence. The patient in that report had another resection, after which there was no further recurrence. To our knowledge, there are no other case reports of a deep soft tissue JXG with aggressive recurrence.

Lessons for the Clinician

- Fibrohistiocytic tumors should be included in the differential diagnosis of deep soft tissue masses. Juvenile xanthogranuloma is the most common fibrohistiocytic tumor.
- Juvenile xanthogranuloma may present without skin lesions.
- Most juvenile xanthogranulomas regress spontaneously. Treatment may be needed in cases of clinical compromise, and can include resection, steroids, or chemotherapy.
- The absence of CD1a and S100 protein on immunohistochemistry can help exclude Langerhans cell histiocytosis.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Recognize the imaging features of extrapulmonary causes of respiratory distress.

- Know the clinical features of an infant with airway obstruction.
- Know the clinical manifestations and approaches to therapy of neck masses in the newborn infant.

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Index of Suspicion in the Nursery

3

Sudden Unexpected Collapse in a Full-term Infant

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PRESENTATION

A 3,040-g appropriate-for-gestational age girl is delivered vaginally at 38 weeks by an 18-year-old primigravida following induction of labor for preeclampsia. Pregnancy complications included obesity and elevated maternal serum α -fetoprotein without open neural tube defect on ultrasonography. The mother had received 2 g/hour of magnesium sulfate during labor. The infant's Apgar scores are 8 and 9 at 1 and 5 minutes, respectively, and she requires routine postdelivery care. The resuscitation team notes normal physical examination findings, including appropriate tone and intact spine, and the infant remains with her mother. At 90 minutes after birth, she is lying skin to skin on her mother's chest after attempting breastfeeding and is found by her nurse to be pale, limp, and apneic. She is placed on a radiant warmer, positive pressure ventilation is initiated, and the NICU team is called.

On arrival, the NICU team finds the neonate to have cyanosis, hypotonia, and apnea. Her heart rate is 60 beats/min. Despite improvement with positive pressure ventilation, the infant requires intubation for persistent apnea. On physical examination, she is stuporous with no spontaneous activity, and has absent primitive reflexes, flaccid tone, and sluggish pupils. She is admitted to the NICU for management of respiratory failure and neonatal encephalopathy. Her initial arterial blood gas demonstrates severe metabolic acidosis (pH 7.00/pCO₂ 35/pO₂ 124/HCO₃ 9/base deficit -23, lactate 14.9 mg/dL [1.7 mmol/L]). Comprehensive metabolic panel is normal except for low serum carbon dioxide (14 mEq/L [14 mmol/L]) and elevated magnesium (4.7 mg/dL [2.35 mmol/L]). She receives mechanical ventilation and whole-body therapeutic hypothermia is initiated. Umbilical lines are placed. She receives antibiotics for suspected sepsis; blood culture remains negative. Metabolic acidosis resolves after she receives normal saline and sodium bicarbonate boluses. Complete blood cell count is significant only for mild anemia (hemoglobin 11.5 g/dL [115 g/L]). Serum ammonia is normal. Cranial ultrasonography shows no acute hemorrhage. Echocardiography demonstrates normal structure and biventricular function.

DISCUSSION

Progression

At 18 hours after birth, the neonate's abdomen becomes distended, and a 10F Replogle suction tube is placed, which has a nonbilious output of less than 10 mL/kg per day. Figure 1 depicts the abdominal radiograph after Replogle tube placement.

AUTHOR DISCLOSURE Drs Aghion, Falck, and Sundararajan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

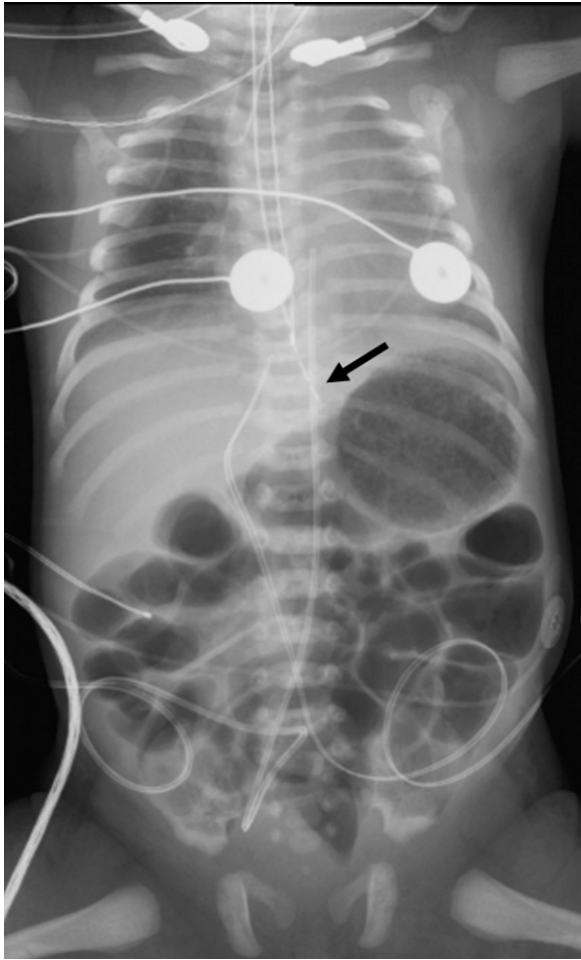


Figure 1. Chest and abdominal radiograph showing the tip of the Replogle tube terminating above the gastric bubble (black arrow) with diffuse gaseous distention of the bowel.

Differential Diagnosis

- Airway obstruction due to:
 - Accidental suffocation
 - Hypotonia due to hypermagnesemia
- Aspiration secondary to:
 - Esophageal stricture
 - Esophageal web
 - Esophageal atresia
 - Neonatal achalasia

Diagnosis

The infant undergoes therapeutic hypothermia for 72 hours and is extubated on day 2 after birth. The Replogle tube remains malpositioned above the stomach. Upper gastrointestinal contrast study on day 6 after birth shows fixed narrowing at the gastroesophageal (GE) junction, which is concerning for stenosis (Fig 2A). Upper gastrointestinal endoscopy and esophageal dilation are performed on day 10 after birth, ruling out atresia and making stricture less

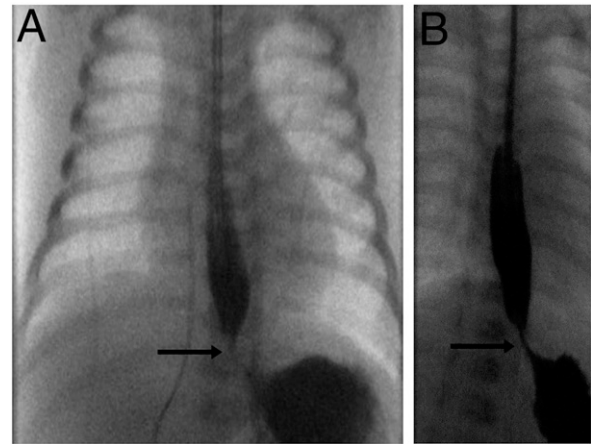


Figure 2. A. Upper gastrointestinal contrast study illustrates the fixed narrowing at the gastroesophageal junction (black arrow) concerning for stenosis. B. Esophagogram obtained after esophageal dilation illustrating the persistent severe narrowing (bird's beak appearance) at the gastroesophageal junction (black arrow), despite contrast now passing readily into the stomach, suggestive of neonatal achalasia.

likely. Subsequent esophagography on day 13 after birth shows persistent severe narrowing at the GE junction (Fig 2B) concerning for neonatal achalasia. On day 15 after birth, esophagogastroduodenoscopy is performed. Biopsy of the GE junction shows minimal inflammation of the distal esophagus. Repeat esophagography on day 29 after birth continues to demonstrate persistent severe narrowing at the GE junction consistent with neonatal achalasia. The infant undergoes laparoscopic Heller myotomy on day 34 with complete symptom resolution. She is discharged 6 weeks after birth on full oral feeds. At her 6-month NICU follow-up visit, neurodevelopmental screening result is normal. Sudden unexpected collapse is presumed to be because of aspiration during the first breastfeeding attempt secondary to obstruction of the lower esophageal sphincter (LES) from neonatal achalasia. In the presence of this confirmed anomaly, potential etiologies such as accidental suffocation and hypotonia are less likely to be the primary cause of this event. We believe this is the first report of neonatal achalasia presenting as sudden unexpected collapse in the immediate newborn period.

The Condition

Neonatal achalasia is a neuromuscular disorder of esophageal motility characterized by failure of relaxation of the distal esophagus. (1)(2) Achalasia occurs in 0.5 to 1 in 100,000 infants; it is uncommon in children (3%–5%) and extremely rare in neonates (<0.5%). (2)(3) Achalasia is associated with conditions such as trisomy 21, congenital hypoventilation syndrome, eosinophilic

esophagitis, familial dysautonomia, and achalasia-alacrima-adrenocorticotrophic hormone insensitivity syndrome. (1) The pathophysiology involves deterioration of the inhibitory myenteric plexus innervating the LES and esophageal body. (1) This creates a disparity between inhibitory and excitatory neurons, leading to absent peristaltic activity in the esophageal body, elevated LES resting pressures, and lack of LES relaxation with swallowing. (1) Clinical presentation typically includes emesis, recurrent aspiration pneumonia, nocturnal cough, hoarseness, and feeding issues. (1)(2)(4) Neonates with achalasia could also present with feeding difficulties shortly after birth that result in sudden unexpected collapse from pooled secretions as occurred in our infant.

Acute cardiorespiratory compensation resulting in sudden unexpected collapse could also represent a symptom of a previously undiagnosed condition, such as congenital heart disease, pulmonary hypertension, pneumonia, inborn error of metabolism, or hypermagnesemia from maternal medication. (5)(6) The other listed diagnoses were excluded with radiography, echocardiography, and serial laboratory blood tests. The episode of unexpected collapse occurred under clinical observation while the mother was attempting to breastfeed her infant with nursing assistance, therefore, accidental suffocation or foul play was excluded as a possible etiology. Membranous esophageal atresia, an extremely rare subtype of esophageal atresia could also present with drooling of saliva and frothing in the early newborn period. (7) However, radiologic findings will include paucity of bowel gas on plain radiography with demonstration of an atretic esophageal pouch on esophageal contrast study. (7)

Confirmatory diagnostic studies for achalasia include fluoroscopic examinations, such as modified barium swallow or esophagography, and esophageal manometry. Esophagography findings include a dilated proximal esophagus with classic “bird’s beak” tapering of the distal esophagus. (1)(2)(4) Esophageal manometry demonstrates elevated resting LES pressure, absent or low-amplitude peristalsis, or nonrelaxing LES on swallowing. (1)(2) Medical management includes nifedipine, botulinum injection, or pneumatic dilation. (1)(4) Surgical options for achalasia include laparoscopic Heller myotomy, in which the esophageal muscle is longitudinally incised approximately 5 cm above the GE junction, extending 2 to 3 cm into the cardia of the stomach, (1)(4) or per oral endoscopic myotomy, with the youngest reported patient being 3 years old. (1) In conclusion, neonatal achalasia, a rare entity in

infants, requires a high index of suspicion for diagnosis in the immediate newborn period. Prompt early diagnosis and surgical treatment of the mechanical obstruction is curative.

Lessons for the Clinician

- Achalasia is a neuromuscular esophageal disorder that is uncommon in infancy and may occur in isolation or with other anomalies or syndromes.
- Symptoms of achalasia typically include feeding intolerance, vocalization abnormalities, and recurrent aspiration. An atypical symptom is feeding difficulty soon after birth that could result in sudden unexpected collapse from pooled oral secretions.
- Diagnosis is confirmed in neonates and children via esophagography.
- Treatment options include medications, pneumatic dilation, and surgical management with laparoscopic Heller myotomy.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Breastfeeding.
- Know the indications for assisted ventilation, including continuous positive airway pressure, immediately after birth and how to assess its effectiveness.
- Know the factors affecting and regulating the systemic circulation in the fetus (including umbilical vessels) and newborn infant during the perinatal transitional period.

ACKNOWLEDGMENT

We would like to thank Dr Jane S. Kim at University of Maryland School of Medicine for her assistance with the diagnostic radiology studies.

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Case 3: Sudden Unexpected Collapse in a Full-term Infant

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Case 3: Sudden Unexpected Collapse in a Full-term Infant

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Index of Suspicion in the Nursery

1 Term Infant with Abdominal Distention and Refractory Hypertension

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AUTHOR DISCLOSURE Dr Ji and Ms Kudalmana have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male neonate is born at an estimated 37 3/7 weeks' gestation via emergent repeat cesarean section to a 25-year-old gravida 6, para 5 Hispanic mother. Pregnancy, labor, and delivery complications include oligohydramnios, decreased fetal movement, non-reassuring fetal status with fetal tachycardia and minimal variability, and meconium-stained amniotic fluid on delivery. The neonate is "stunned" on presentation with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively, with a birthweight of 2,929 g. He was admitted to the NICU for further evaluation and management of abdominal distention.

On examination, the neonate is found to have moderate abdominal distention and firmness, hypoactive bowel sounds, brown fluid produced from oral suctioning, similar brown fluid produced from urethral opening, patent anus, hypoplastic nails, and a short hallux of the left foot. The remainder of the examination findings are unremarkable. Kidneys, ureters, and bladder (KUB) are examined because of the abdominal distention, and showed a gasless abdomen with a small gastric bubble. Abdominal ultrasonography is then conducted because of an inability to view the liver and spleen, which showed findings of moderate ascites. The ascites with the combination of pulmonary edema on chest radiography gave rise to a concern for hydrops fetalis (Fig).

DISCUSSION

Diagnosis

Further concern for malrotation and volvulus with continued abdominal distention and progressive bluish hue on the abdomen led to an upper gastrointestinal study with small bowel follow-through, the result of which was normal. Exploratory laparotomy was conducted on day 2 after birth, which uncovered a frank perforation at the distal ileum. An 8-cm small-bowel resection with ileostomy and mucous fistula was performed. After 5 days of enteral feeds, the neonate showed resistance and disinterest to feeds with recurrent emesis. Repeat abdominal ultrasonogram, head ultrasonogram, and KUB radiograph were all normal. The neonate started showing interest in feeds after making a transition to an amino acid–based infant formula. On day 50, the neonate underwent bowel reanastomosis with gradual advancement of feeds to full feeds by day 62.

The neonate was noted to have intermittent periods of hypertension in the setting of feeding intolerance on day 13 after birth. The incidence of neonatal hypertension ranges from 0.2% to 3% with the differential including renovascular (thromboembolism, renal artery stenosis, midaortic coarctation, compression of



Figure. Computed tomography angiography showing abdominal aortic narrowing.

renal artery, idiopathic arterial calcification, congenital and acquired causes), pulmonary (bronchopulmonary dysplasia, pneumothorax), cardiac (thoracic aortic coarctation), endocrine (congenital adrenal hyperplasia, hyperaldosteronism, hyperthyroidism), medications, neoplasia (Wilms tumor, neuroblastoma, pheochromocytoma, mesoblastic nephroma), neurologic (intracranial hypertension, pain, subdural hematoma), and miscellaneous (adrenal hemorrhage, hypercalcemia, nephrocalcinosis, total parenteral nutrition) causes. (1) Echocardiography was conducted to rule out congenital heart diseases, with the results showing normal cardiac function. After negative urinalysis findings and normal renal ultrasound scan, nephrology recommended starting isradipine with gradual increase in dose for a blood pressure goal of less than 100/60 mm Hg. He was given intermittently trials of hydralazine on day 50 without effect. Isradipine was then restarted without improvement, resulting in a medication switch to captopril on day 53. Repeat renal ultrasonography on day 66 showed normal renal morphology with slightly elevated flow velocity at the origin of the left renal artery. Peripheral velocities are symmetric, with the right kidney and resistive indices being within normal limits. As part of the hypertension workup, renin, aldosterone, and cortisol levels were checked, results of which were within normal limits. Chromosome microarray analysis results were negative as well.

Given the history of intestinal perforation and refractory hypertension, the nephrologist recommended computed tomography angiography, which revealed the diagnosis of midaortic syndrome. Amlodipine was then started with greater control of hypertension, leading to discontinuation of captopril on day 81.

The neonate was discharged from the hospital on day 84 with labetalol and amlodipine, with well-controlled blood

pressure. He was closely followed by the nephrology and surgery teams.

The Condition

Midaortic syndrome is a rare condition found in children and young adults that is characterized by segmental narrowing of the abdominal aorta with involvement of the major branches. (2)(3)(4) It is most often congenital because of irregularity with the fusion and maturation of the embryonic dorsal aortas during development, but acquired causes include neurofibromatosis, fibromuscular dysplasia, Williams syndrome, retroperitoneal fibrosis, giant cell arteritis, mucopolysaccharidosis, and other in utero insults to the developing aorta. (3)(5) It can present with fetal findings of hydrops fetalis, growth restriction, and polyhydramnios. (4)

Midaortic syndrome has a diverse presentation that includes refractory hypertension, failure to thrive, abdominal bruit, diminished arterial pulses of the lower extremities, congestive heart failure, cardiomyopathy, and renal dysfunction. (4) Symptoms are usually secondary to hypertension, but claudication and intestinal ischemia may be present. (2) This is seen in the current case, in which the patient presented with intestinal perforation due to ischemia as the primary problem.

Hypertension is usually difficult to control with chronic malignant hypertension being the cause of most of the complications associated with this syndrome. The preferred diagnostic test for midaortic syndrome is angiography of the descending and abdominal aorta. (3)(4) The goal of treatment is to normalize the patient's blood pressure to avoid complications secondary to hypertension, preserve renal function, and resolve claudication by using approaches that include pharmacotherapy, endovascular treatment, and surgical intervention. (3)(5)(6) Surgical therapy has been shown to be curative in most patients and has become the treatment of choice, (3)(5) but antihypertensive medication can be used as a bridge to surgery, especially for neonates.

Lessons for the Clinician

- Midaortic syndrome should be in the differential diagnosis in pediatric cases of intestinal ischemia with perforation and refractory hypertension.
- The gold standard for diagnosis of midaortic syndrome is angiography of the aorta with either computed tomography or magnetic resonance imaging.
- Surgical therapy has been shown to be the treatment of choice, but antihypertensive pharmacotherapy can be used to bridge surgery, especially for neonates.

ACKNOWLEDGMENTS

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American Board of Pediatrics Neonatal-Perinatal Content Specification

- Formulate a differential diagnosis for an infant with systemic hypertension in early infancy.

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Index of Suspicion in the Nursery

1 Term Infant with Intractable Seizures and Bilateral Hydronephrosis

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AUTHOR DISCLOSURE Drs Bauer, Wright, Rice, and Ikonomidou have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male neonate is born via vaginal delivery at 37 1/7 weeks' gestation to a healthy 30-year-old gravida 3, para 2 mother. The pregnancy had been complicated by polyhydramnios, severe fetal hydronephrosis, anti-Kell antibodies, and questionable fetal mega cisterna magna. Labor is induced secondary to worsening bilateral fetal hydronephrosis. The delivery is uncomplicated and Apgar scores are 9 and 9 at 1 and 5 minutes, respectively. Initial physical examination findings are significant only for left-sided club foot, and the infant is admitted to the well-newborn nursery. State newborn screening is performed 24 hours after birth, results of which are normal.

There is no significant familial history of congenital neurologic or urologic abnormalities, and both previous children of these parents are healthy. Amniocentesis performed during this pregnancy secondary to the bilateral fetal hydronephrosis had revealed a normal fetal microarray.

The infant is admitted to the NICU 3 days after birth secondary to hypernatremia (150 mEq/L [150 mmol/L]) and severe (grade 4) bilateral hydronephrosis confirmed with postnatal ultrasonography. While in the NICU, the neonate is noted to have episodes of lateral eye deviation, bilateral arm and leg twitching, and episodes of apnea. Electrolytes (excluding hypernatremia), glucose, and cranial ultrasonography findings are normal. A sepsis evaluation is completed and the infant is treated for 48 hours with ampicillin, cefotaxime, and acyclovir until blood, urine, and cerebrospinal fluid cultures return negative. Amplitude-integrated electroencephalography (EEG) findings are concerning for seizure activity and video EEG shows frequent multifocal epileptiform activity in both hemispheres indicative of abnormal cortical hyperexcitability, lowering the threshold for seizures. Following consultation with pediatric neurology he receives a loading dose of levetiracetam and maintenance therapy is initiated. Brain magnetic resonance imaging (MRI) reveals trace right occipital subarachnoid hemorrhage and trace infratentorial posterior fossa subdural hematoma thought to be secondary to birth trauma and not related to the seizure activity. Throughout the rest of the first week after birth, he has no further clinical seizure activity while receiving a maintenance dose of levetiracetam, and is able to take oral feeds of breast milk and formula.

In the meantime, further urologic evaluation is performed. Voiding cystourethrogram findings are normal, and mercaptoacetyltriglycine renogram with furosemide diuresis confirms bilateral ureteropelvic junction obstruction. Bilateral nephrostomy tubes are placed for renal decompression and plans are made for future

bilateral ureteroplasty. Erythropoietin injections are started for preventing anemia in the setting of renal disease, and the neonate continues to receive prophylactic amoxicillin because of his severe bilateral hydronephrosis.

DISCUSSION

Progression

Following nephrostomy tube placement, the infant was again noted to have increasing frequency of apnea spells, and video EEG identified frequent seizure activity. Levetiracetam dosing was increased, and a loading dose of phenobarbital was administered, followed by maintenance with continued escalation of seizure frequency. Because of persistent and increasing seizure activity, further antiepileptic treatments were administered in an attempt to improve seizure control; these included vitamin B6, phenytoin, pyridoxal phosphate, leucovorin, topiramate, and carbamazepine, none of which reduced seizure frequency for any extended period. Most of the medications led to a transient favorable response for a few days, but the seizures eventually recurred.

The differential diagnosis for intractable seizures is vast and includes metabolic derangements (hypoglycemia, hyponatremia), infectious diseases (meningitis, sepsis), trauma (intraventricular hemorrhage, subarachnoid hemorrhage), and epileptic syndromes (channelopathies, multiple genetic syndromes). The differential is shorter with more rare associations if the urologic and musculoskeletal abnormalities are included, however this could easily be unrelated. A thorough infectious, neurologic, and genetic evaluation was undertaken. Multiple laboratory tests were performed including blood and urine for pipelicolic acid, organic acids, acylglycines, lysosomal storage disease screen, α -amino adipic semialdehyde, creatine biosynthesis panel, purines and pyrimidines, lactate, pyruvate, long-chain fatty acids, carnitine, acylcarnitine, biotinidase enzymes, and carbohydrate-deficient transferrins, all of which were unremarkable. Cerebrospinal fluid studies including neurotransmitters and amino acids were normal. Repeat brain MRI with magnetic resonance spectroscopy identified punctate loci of T1 and T2 hyperintensities in the right peritrial white matter of unknown clinical significance, but the findings were otherwise unremarkable. Ophthalmology evaluation was normal.

Diagnosis

After receiving the unremarkable infectious and metabolic laboratory results, a genetic epilepsy panel was sent to sequence 22 mutations known to cause infantile epilepsies; results showed abnormality for a heterozygous mutation in the *KCNT1* gene. This mutation, specifically coding DNA

c.1420 C>T and amino acid p.Arg474Cys base changes, is associated with an autosomal dominant disorder, malignant migrating focal seizures of infancy (MMFSI), that is known to have a very poor prognosis. This neonate's clinical status continued to worsen, and he ultimately developed intractable seizures despite multiple antiepileptic therapies. The family decided to redirect the goals of care to focus on comfort and allow natural disease progression. The antiepileptic medicines were discontinued and he died 2 days later.

Condition

Neonatal seizures occur in 2.6 per 1,000 newborns and the frequency increases with prematurity and low birthweight. (1) Seizures in neonates may be clonic, tonic, myoclonic, or subtle and may present with lip smacking, abnormal eye movements, stereotypic movements such as bicycling, or central apnea. Most neonatal seizures are symptomatic and are caused by infections, metabolic derangements, structural central nervous system abnormalities, stroke, or hypoxic-ischemic encephalopathy. Genetic epilepsy syndromes become the focus of the diagnostic evaluation if infectious, structural, and metabolic evaluations have been unrevealing. Multiple genes have been associated with genetic epilepsy syndromes including *KCNQ2*, *KCNQ3*, *SCN1A*, *SCN9A*, *GABGR2*, and *KCNT1*. (2)

The *KCNT1* gene encodes a sodium-activated potassium (KNa) channel expressed throughout the nervous system, which regulates hyperpolarization after repetitive neuronal firing. (3) Multiple *KCNT1* gene mutations have been described and are considered causative for infantile epileptic encephalopathy syndromes. (2)(4) Two distinct seizure disorders, MMFSI and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), have been associated with gain-of-function mutations in *KCNT1*. (5) Patients with ADNFLE tend to have clusters of short motor seizures during sleep that are also associated with intellectual disability and psychiatric disorders, though seizures are not typically observed in infants. (6)

This patient's clinical course was most consistent with MMFSI, given the migrating focal seizures that were intractable to treatment. Previous cases have reported similar neurologic findings, including apnea caused by seizures and video EEG findings of asynchronous multifocal spikes through both cerebral hemispheres (Table). (3)(6) To our knowledge, this is the first reported case of a patient with MMFSI and a *KCNT1* mutation to present with urologic abnormalities.

Genetic testing in this patient confirmed the base change c.1420C>T inducing the amino acid change p.Arg474Cys, which is highly conserved among species in the *KCNT1*

TABLE. **Clinical Features of Patients with c.1420C>T *KCNT1* Mutations**

CLINICAL FEATURE	CURRENT PATIENT	PATIENT OF OHBA ET AL (6)	PATIENT OF SHIMADA ET AL (3)
Sex	M	M	M
Amino acid change	p.Arg474Cys	p.Arg474Cys	p.Arg474Cys
Age at seizure onset	3 days	0 days	9 days
Seizure type	Apnea eye deviations, tonic convulsions	Facial flushing eye deviations, tonic convulsions	Apnea, focal motor tonic convulsions
MRI findings	Right occipital SAH, infratentorial SDH (4 days of age)	Delayed myelination thin CC (6 months of age)	Delayed myelination thin CC (6 months of age)
EEG findings	Bilateral multifocal spikes, abnormal cortical, hyperexcitability	Bilateral multifocal spikes, suppression burst	Bilateral multifocal spikes
Non-neurologic findings	Club foot bilateral HN, UPJ obstruction	None described	None described
Intellectual disability	N/A	Yes	Yes

Arg=arginine; Cys=cysteine; CC=corpus callosum; EEG=electroencephalography; HN=hydronephrosis; MRI=magnetic resonance imaging; N/A=not applicable; SAH=subarachnoid hemorrhage; SDH=subdural hematoma; UPJ=ureteropelvic junction.

gene. Another neonate affected with the same *KCNT1* mutation had a brain MRI at 6 months of age, which demonstrated delayed myelination and a thin corpus callosum. (3) Another *KCNT1* mutation at p.Arg474 encoding histidine instead of cysteine secondary to DNA coding changes at c.1421G>A had similar clinical neurologic symptoms as seen in the current patient. (2) No previous patient with mutations in p.Arg474 had abnormal urologic findings.

Mutations found in the *KCNT1* gene induce learning impairment, psychiatric disorders, cardiac arrhythmias, sleep apnea, gastroesophageal reflux disease, microcephaly, spastic quadriplegia, and choreiform movements. (5)(6) EEG in patients with MMFSI shows epileptic spikes that migrate throughout multiple foci, often becoming more frequent as the patient ages, and tend to be resistant to antiepileptic pharmacotherapy. Treatment of these patients with multiple antiepileptic therapies (phenobarbital, carbamazepine, levetiracetam, lamotrigine, valproic acid, topiramate, clonazepam, clobazam, phenytoin, zonisamide, vigabatrin, intravenous immunoglobulin, adrenocorticotrophic hormone, gabapentin, and the ketogenic diet) have been ineffective and all these children have significant developmental delay with frequent seizures. (6) Pharmacologic studies evaluating quinidine or ezogabine have shown some promise in decreasing seizure frequency for a period, but current studies have not shown significant improvement in developmental milestones. (7)(8)

The bilateral ureteropelvic junction obstruction leading to hydronephrosis in the current patient is an original finding in a patient with a confirmed *KCNT1* mutation. It is not clear if the *KCNT1* mutation is causative because there is no literature suggesting an association of this potassium channel and urothelial or renal cell development. Another potassium channel *KCNJ1* has been implicated in Bartter syndrome type 2, an electrolyte-losing nephropathy. However, this particular potassium channel does not appear to be present in the nervous system, nor is there a clear overlap with *KCNT1*. (9) This patient did not undergo whole exome sequencing to determine if other mutations were present that could have caused the abnormal urologic findings. As part of the evaluation in a patient with intractable seizures, renal ultrasonography should be considered to screen for urologic abnormalities potentially associated with genetic epilepsy syndromes.

Lessons for the Clinician

- When multiple congenital anomalies are known, it is important for the clinician to be aware of potential comorbidities in other organ systems.
- After the initial evaluation aimed at excluding infectious, metabolic, or structural abnormalities in intractable seizures, genetic epilepsy syndromes including channelopathies should be considered.

- Continued discussion with the family of a neonate with a genetic diagnosis that has a poor prognosis is important to determine the family's goals of care for their child.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Understand the differential diagnosis and evaluation of neonatal seizure.

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Case 1: Term Infant with Intractable Seizures and Bilateral Hydronephrosis

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Case 1: Term Infant with Intractable Seizures and Bilateral Hydronephrosis

Adam S. Bauer, C. Lydia Wraight, Gregory M. Rice and Chrysanthi Ikonomidou

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Index of Suspicion in the Nursery

2 Term Male Infant with Persistent Apneic Episodes

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AUTHOR DISCLOSURE Ms Kudalmana and Dr Ji have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male neonate is born at an estimated 41 3/7 weeks' gestation via vacuum-assisted vaginal delivery to a 27-year-old gravida 4, para 1 Hispanic woman. She had pregnancy-induced hypertension with her previous pregnancy. Significant family history includes a maternal uncle with seizures due to traumatic brain injury and maternal grandmother with seizures from brain tumor. Labor and delivery complications include nonreassuring fetal status with decelerations and meconium-stained amniotic fluid. The neonate's birthweight is 3,671 g and Apgar scores are 6 and 8 at 1 and 5 minutes, respectively. The neonate is "stunned" on presentation, with a weak cry, shallow breathing, and hypotonic appearance. He requires stimulation with continuous positive airway pressure support at delivery and admission to the NICU for respiratory distress.

On examination, he is sleepy but responsive. He presents with caput with normal head size, normal chest expansion symmetrically with equal breath sounds, and slight decreased tone. The remainder of the examination findings are unremarkable. Complete blood cell count and blood culture after admission show negative results after receiving 36 hours of antibiotics. The neonate continues to have multiple apneic episodes with hypoxemia, hypotonia, inconsistent weight gain, and stagnant fronto-occipital circumference. Cerebrospinal fluid shows normal cell counts, thus excluding meningitis. His initial findings on head ultrasonography and electroencephalography are normal, with no signs of seizure activity.

DISCUSSION

Diagnosis

The differential diagnosis for apnea in newborns is very broad. In term infants, apnea has several causes, including temperature instability, neurologic (birth trauma, medications, hemorrhage, seizures, central nervous system malformations), pulmonary (respiratory distress syndrome, pneumonia, pulmonary hemorrhage, anatomic malformation), cardiac (congenital heart malformation/disease, increased vagal tone), gastrointestinal (gastroesophageal reflux, abdominal distention), hematologic (anemia), infectious (sepsis, meningitis, necrotizing enterocolitis), metabolic (hypoglycemia, hypo/hypernatremia), inborn errors of metabolism, and genetic factors. (1)

Neurology recommendations for this infant included magnetic resonance imaging, which showed unremarkable results with chromosomal studies. On day 17, the neonate received formal airway evaluation due to concern for

obstructive apnea, with results showing no airway malformations. On day 27 after birth, sleep study conducted due to concern for central sleep apnea demonstrated markedly severe pediatric sleep-disordered breathing with marked oxygenation instability and sleep hypoventilation. *CCHS-PHOX2B* genetic testing revealed no abnormality for congenital central hypoventilation syndrome.

Chromosome microarray revealed the diagnosis. Results showed abnormal 0.054 Mb loss of chromosome band Xq28, including part of Methyl CpG-binding protein 2 (*MECP2*) gene. This is characteristic of Rett syndrome, with the neonate considered to have *MECP2*-related neonatal encephalopathy.

On day 46, he was discharged from the hospital on nasogastric tube feeds and oxygen support.

The Condition

Rett syndrome is a progressive neurodevelopmental disorder that was believed to be exclusive to girls. In classic or typical Rett syndrome, patients have a normal neonatal period with standard developmental milestones being met between 6 and 18 months of age. (2) After this stage, patients start showing the characteristic signs and symptoms of head growth arrest, autistic features, and loss of acquired motor and language skills with stereotypic hand movements. (2)(3) Atypical Rett syndrome is differentiated as the preserved speech, early seizure, and congenital variants. (4)

MECP2 is an X-linked gene, with mutations accounting for most cases. Girls with Rett syndrome are normally heterozygous for the *MECP2* mutation with random X-chromosome inactivation, which led to the thought that this mutation was lethal in boys. (5) In boys, *MECP2* mutations are now known to produce a broad continuum of neurologic symptoms ranging from mild mental handicap to severe neonatal encephalopathy. (2)(6) Other clinical manifestations in boys include hypotonia, microcephaly, respiratory irregularities, seizures, gastrointestinal problems, and growth restriction. (7)(8)

Due to the multisystem involvement seen in Rett syndrome, there are no current targeted therapies for this disorder. Emphasis is being placed on preventive care, including nutritional management, monitoring for gastrointestinal problems, and rehabilitation therapies. Symptomatic management includes drug therapies, such as

antiepileptic drugs for seizures and selective serotonin uptake inhibitors for behavioral issues. (8)

Lessons for the Clinician

- Apnea in a term infant has a wide differential diagnosis including genetic disorders.
- Clinicians should appreciate that signs and symptoms of Rett syndrome can occur on a spectrum, especially in boys.
- Medical management focuses on preventive and symptomatic care.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the significance of persistent neuromotor abnormalities in infancy (including asymmetries).

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Index of Suspicion in the Nursery

3 Term Neonate with Respiratory Distress

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AUTHOR DISCLOSURE Drs Dumpa, Gupta, Iqbal, and Nair have disclosed no financial relationships relevant to this article. Dr Nair is supported by NICHD grant 1R03HD086531-01A1. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is born at 39 weeks to a 21-year-old primigravida with an unremarkable antenatal history and good prenatal care. The Apgar scores are 6, 7, and 8 at 1, 5, and 10 minutes, respectively. Physical examination reveals an appropriate-for-gestational age 3.3-kg term infant with grunting, tachypnea, and intercostal retractions. Decreased air entry is noted over the right side of the chest. A grade 2/6 systolic murmur is heard over the left sternal border with normal heart sounds and good peripheral pulses. The rest of the physical examination findings are within normal limits except for a right-sided small ear tag. The neonate requires positive pressure ventilation initially in the delivery room and then is placed on continuous positive airway pressure (CPAP) at 30% fraction of inspired oxygen. Chest radiography shows near-complete opacification of the right thorax with mass effect and normal lung markings on the left (Fig 1). Due to worsening respiratory distress, she undergoes intubation and is transferred to the regional perinatal center for diagnosis and management.



Figure 1. Anteroposterior view radiograph of chest and abdomen at birth showing near-complete opacification of the right thorax.

Differential diagnoses considered at this point for unilateral lung field opacity with mass effect include right-sided diaphragmatic hernia, congenital pulmonary airway malformation, pulmonary sequestration, or a space-occupying lesion like a tumor. Ultrasonography of the chest shows a large, solid mass in the right thorax with an intact diaphragm, an abnormality consistent with consolidated lung or a tumor (Fig 2).

DISCUSSION

Diagnosis

Computed tomography (CT) of the chest reveals the diagnosis (Figs 3 and 4). An aberrant left pulmonary artery (LPA) is seen arising from the right pulmonary artery consistent with an LPA sling. A severely stenotic right main bronchus at its origin and a possibly atretic right upper lobe bronchus are noted.

Case Progression

Given these airway and vascular anomalies, the infant is transferred to a tertiary center with expertise in cardiothoracic surgery. Repair of the anomaly includes reimplantation of the LPA to the main pulmonary artery and ligation of the ductus arteriosus. No atresia of the bronchus is noted intraoperatively as the right lung inflated well once the sling was repaired. The neonate undergoes extubation on postoperative day 3 and is transferred back to the referring center on CPAP. She is subsequently weaned to room air by 4 weeks after birth. Genetic evaluation reveals no other anomalies. Microarray is offered and recommended but deferred by the family.

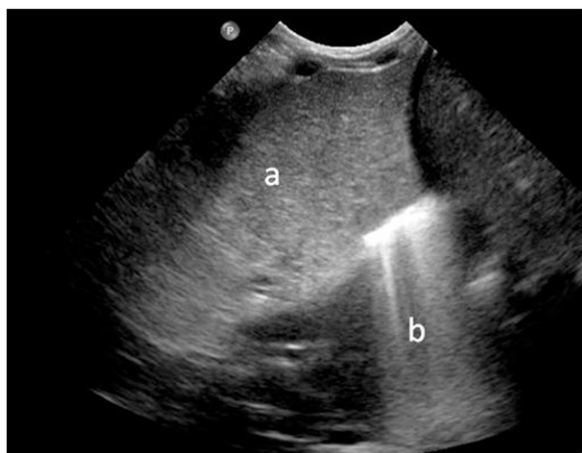


Figure 2. Ultrasound scan of the chest, right thorax with A) a large mass on the right, consistent with a consolidated lung with an intact diaphragm, and B) liver.

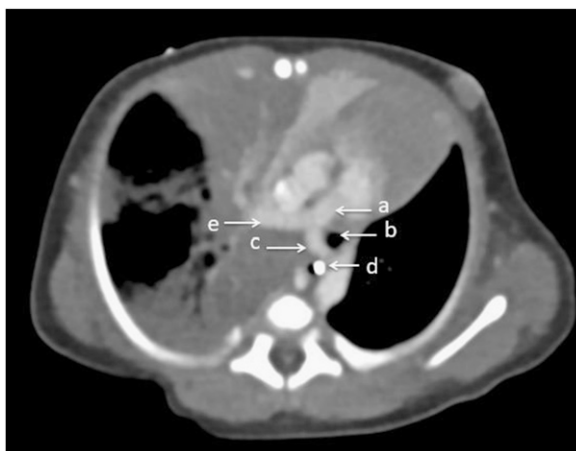


Figure 3. Axial view of chest computed tomography scan showing A) main pulmonary artery, B) trachea, C) left pulmonary artery with an abnormal origin from the right branch instead of the main pulmonary artery looping around the trachea forming a "sling," D) esophagus with enteric tube, and E) right pulmonary artery.

The Condition

LPA sling is a rare congenital vascular anomaly in which the LPA arises from the posterior aspect of the right pulmonary artery, coursing over the right main bronchus and then posteriorly between the trachea and esophagus to reach the left lung, forming a sling around the trachea. LPA sling is often associated with congenital tracheal stenosis.

First reported in 1897 by Glaevecke and Doehle, the term vascular sling was used by Contro et al in 1958

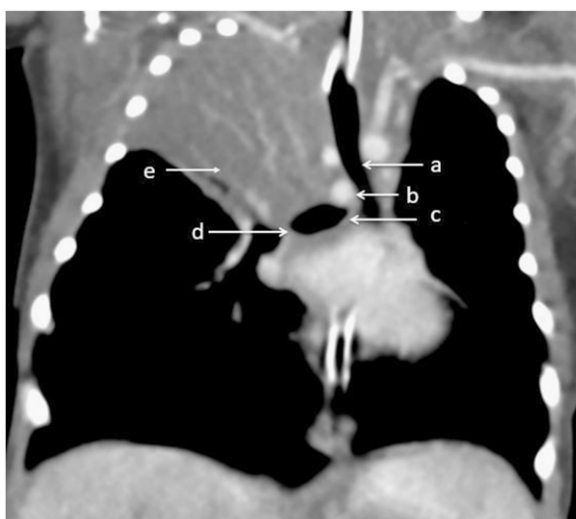


Figure 4. Coronal view of chest computed tomography scan showing A) trachea, B) left pulmonary artery with an abnormal course around the trachea at its bifurcation, causing stenosis of the right bronchus, C, D) areas of stenosis of the right main bronchus, and E) atelectatic upper lobe of the right lung.

to distinguish it from vascular ring. (1)(2) Later, Berdon et al introduced the term “ring-sling complex” with description of the associated airway anomalies. (3) The first surgical correction was performed by Potts in 1958. (2) The exact incidence is not reported because of the rarity of the condition. Infants can present with varying degrees of respiratory distress within the first few weeks to months after birth. Although symptoms are noted early, they are usually attributed to other causes. In the current case, the near-complete opacification and mass effect of the right lung prompted appropriate imaging, which led to an early diagnosis. An LPA sling presenting as a unilateral lung anomaly may also be detected during antenatal ultrasound screening. (4) In our patient, antenatal ultrasonography did not reveal any anomaly. The signs and symptoms depend on the extent of airway involvement. Compression of the bronchus causes atelectasis or hyperinflation (ball valve mechanism). Tracheal compression can result in wheezing, stridor, or severe respiratory compromise. Occasionally, dysphagia and failure to thrive can be seen. Patients can be asymptomatic initially and present with symptoms in older childhood or as adults. LPA sling is associated with various cardiac and noncardiac abnormalities. Common cardiovascular associations include atrial septal defect, ventricular septal defect, tetralogy of Fallot, coarctation of aorta, and patent ductus arteriosus. Extracardiac anomalies include vertebral defects, anal atresia, tracheoesophageal fistula, renal anomalies, and limb abnormalities (VATERL), biliary atresia, absent gall bladder, Hirschsprung disease, and imperforate anus. (5)

The diagnosis of LPA sling is primarily radiologic. A chest radiograph can reveal right-sided hyperinflation or atelectasis, indentation of the trachea, tracheal narrowing, and right-sided tracheal bronchus. An esophagram is of limited value but can show an indentation anterior to the esophagus. Echocardiography can establish the diagnosis of pulmonary sling and delineate other associated cardiac anomalies. CT and magnetic resonance imaging (MRI) are the imaging modalities of choice and are useful for planning surgical management. CT has an advantage over MRI because of better visualization of lung parenchyma, faster scanning time, and lower requirement for sedation, but has the disadvantage of exposure to ionizing radiation. CT angiography gives the most information. (6) The degree of tracheal stenosis is best assessed with bronchoscopy.

Management

Management is based on the clinical symptoms and anatomy. Asymptomatic patients are followed clinically.

Symptomatic patients undergo elective or emergent repair depending on clinical stability. The preferred approach for surgical repair is median sternotomy with cardiopulmonary bypass, thus allowing simultaneous repair of other intrathoracic anomalies if present. (7) LPA sling repair involves reimplantation of the LPA onto the main pulmonary artery. Another alternative approach involves translocation of the undivided LPA anterior to the trachea at the time of tracheal resection for congenital tracheal stenosis. (8) Tracheal stenosis is the main comorbid condition that dictates the long-term prognosis in patients with LPA sling. Surgical repair for moderate-to-severe stenosis may include tracheal resection with end-to-end anastomosis, slide tracheoplasty, or patch tracheoplasty. Tracheal resection with end-to-end anastomosis is preferred if stenosis involves a short segment of the trachea (25%–40%). (9) Complications are fewer and the outcomes are better in patients treated with slide tracheoplasty. (10)

Lessons for the Clinician

- A left pulmonary artery (LPA) sling is a rare, congenital vascular anomaly that should be suspected in a neonate with a unilateral lung field opacification. Surgical correction is the treatment when indicated.
- The outcome and prognosis is usually favorable and depends on associated tracheobronchial, cardiac, and extracardiac anomalies.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical features of an infant with airway obstruction.

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Case 3: Term Neonate with Respiratory Distress
Vikramaditya Dumpa, Puneet Gupta, Vaseem Iqbal and Jayasree Nair
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Case 3: Term Neonate with Respiratory Distress

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Index of Suspicion in the Nursery

3 Term Neonate with Tachycardia

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AUTHOR DISCLOSURE Drs Daryani, Shaw, and Venkatnarayan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A male infant is born at 39 weeks to a 27-year-old, gravida 3, para 1, blood group B–negative woman with an uneventful antenatal period and good antenatal care. The birth was via emergency lower-segment cesarean delivery, in view of breech presentation during labor and a birthweight of 3,100 g (appropriate for gestational age). The infant is born with no respiratory effort and bradycardia at birth requiring positive pressure ventilation. He is noticed to have micrognathia and glossoptosis causing airway obstruction and respiratory distress, with associated cleft palate (Figs 1 and 2), suggestive of Pierre Robin sequence. The infant's



Figure 1. Micrognathia.

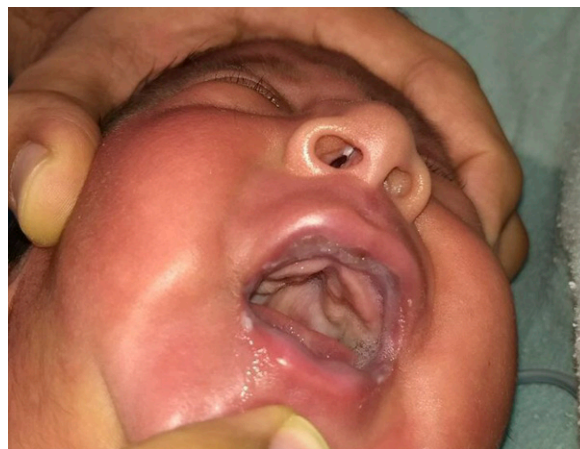


Figure 2. U-shaped cleft palate.

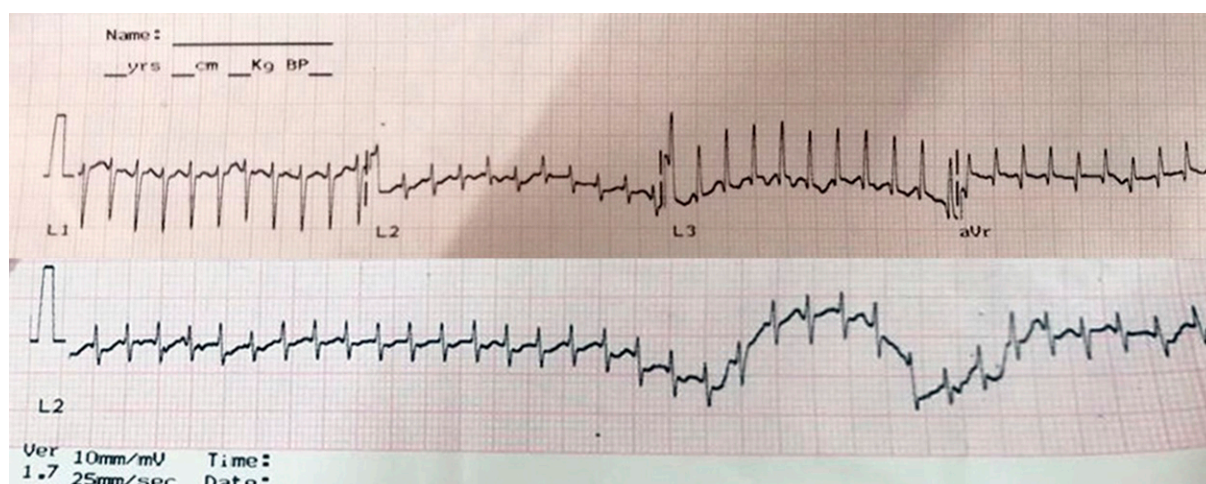


Figure 3. Supraventricular tachycardia.

1-minute Apgar score is 4, and he develops stridor and respiratory distress soon after birth. A nasopharyngeal airway is inserted to relieve the respiratory distress. His 5-minute Apgar score improves to 7, and he is moved to the NICU for observation. He has no other obvious congenital anomaly. His chest radiograph is essentially normal. Approximately 1 hour after birth, he starts having tachycardia, with a heart rate of about 250 beats/minute, and showing features of supraventricular tachycardia on electrocardiography (Fig 3). Adenosine is injected at 100 μ g/kg under cardiac monitoring to terminate the arrhythmia.

DISCUSSION

Progression

At 10 and 11¹/₂ hours after birth, the infant started having tachycardia again, with a heart rate in the range of 200 to 250 beats/min, and adenosine was injected each time to terminate the arrhythmia. His serum electrolytes and calcium were normal, with serum sodium 140 mEq/L

(140 mmol/L; normal range, 133–142 mEq/L [133–142 mmol/L]), serum potassium 3.6 mEq/L (3.6 mmol/L; normal range, 3.5–5.0 mEq/L [3.5–5.0 mmol/L]), and serum calcium 9.8 mg/dL (2.4 mmol/L; 8.0–10.7 mg/dL [2–2.6 mmol/L]). Echocardiography revealed a normal structure except for a 2-mm patent ductus arteriosus with left to right shunt (hemodynamically insignificant). The infant was started on amiodarone treatment (loading dose 5 mg/kg, followed by maintenance infusion and switched to oral therapy on day 3) to prevent further episodes of supraventricular tachycardia. Findings on postarrhythmia termination electrocardiography were suggestive of atrioventricular reentry tachycardia in the form of discernible P waves, RP interval greater than 100 milliseconds, and ST segment depression with absence of δ waves (Fig 4).

Diagnosis/Management

The infant's mother and sibling (5-year-old sister) also have mild mandibular hypoplasia but with no associated cleft palate, glossoptosis, or arrhythmia.

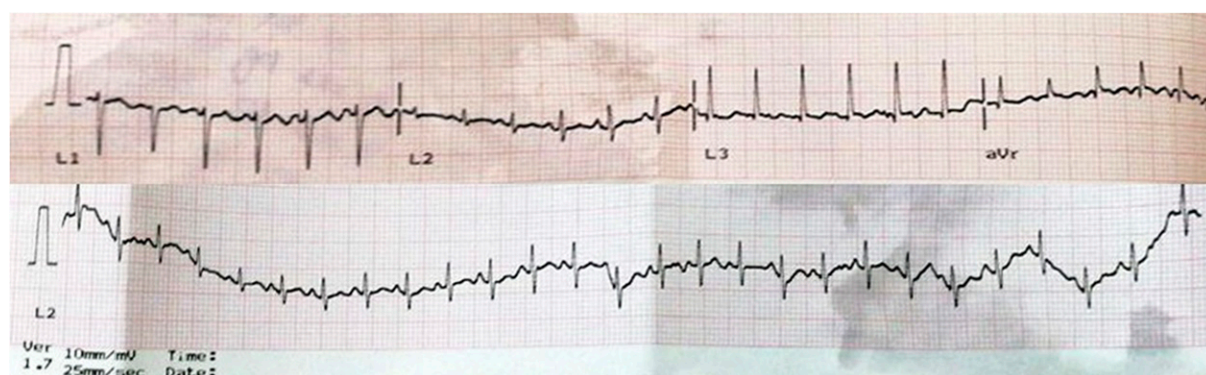


Figure 4. Postadenosine rhythm suggestive of atrioventricular reentry tachycardia.



Figure 5. Missense mutation of COL11A1.

The clinical exome sequencing performed to rule out genetic association revealed autosomal dominant heterozygous missense mutation of the COL11A1 (chr 1:103461555) and SOX9 (chr 17: 70119716) genes (Fig 5). In view of the possibilities of associated campomelic dysplasia (SOX9) and Stickler or Marshall syndrome (COL11A1), a hearing evaluation and eye examination were performed, results of which were normal.

At 1 month of age, the infant underwent elective mandibular distraction in view of airway compromise. On follow-up, at 3 months of age, he was doing well, with no features of airway obstruction and no recurrence of arrhythmia.

THE CONDITION

Pierre Robin sequence (PRS) is a congenital abnormality characterized by micrognathia and glossoptosis, with or without cleft palate, leading to life-threatening respiratory obstruction and feeding difficulties during the neonatal period. (1)

PRS was named after the French stomatologist who, in 1923 and 1934, described the problems associated with newborn micrognathia. Its incidence is estimated to be around 1 in 8,500 to 14,000, (2)(3) but the variability of diagnostic criteria makes it difficult to define precisely.

PRS has been associated with a range of syndromes and chromosomal anomalies, but the underlying pathogenesis of PRS is yet to be fully elucidated. Hypothesized models include a primary failure of mandibular outgrowth or a muscular defect with failure of tongue descent.

More than 40 syndromes with PRS have been described, the most common of which are Stickler syndrome and 22q11.2 deletion syndrome. (4) Stickler syndrome type II is caused by heterozygous mutation in the COL11A1 gene, found on 1p21 chromosome. Marshall disorder is a

similar disorder with respect to phenotype and genotype. The SOX9 gene has also been associated with isolated PRS.

Cardiac arrhythmia in PRS has been described with Andersen-Tawil syndrome (associated with long QT syndrome; KCNJ2 mutation) (1) and in association with BMP2 gene deletion (associated with Wolff-Parkinson-White syndrome). (5)(6)(7)

Lessons for the Clinician

- Pierre Robin sequence is a craniofacial anomaly presenting with varying degrees of micrognathia, cleft palate, and glossoptosis leading to mild breathing difficulty to life-threatening obstructive apnea and feeding difficulties during the neonatal period.
- It may present as an isolated anomaly or part of myriad chromosomal anomalies and syndromes.
- Supraventricular tachycardia is a rare association with Pierre Robin sequence.
- High index of suspicion is required to detect possible pathologic tachycardia in neonates.

ACKNOWLEDGMENT

We acknowledge the contributions of Dr H Ravi Ramamurthy, expert in pediatric cardiology, in the management of this case.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the associations and clinical features and management of macroglossia and hypoplastic mandible, including the Pierre Robin syndrome.

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Acyanotic Congenital Heart Disease: Left-to-Right Shunt Lesions 1. C; 2. D; 3. A; 4. B; 5. C.
Right and Left Ventricular Outflow Tract Obstructive Lesions: 1. A; 2. E; 3. B; 4. D; 5. A.

Case 3: Term Neonate with Tachycardia
Hitesh Daryani, Subhash Chandra Shaw and Kannan Venkatnarayan
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Index of Suspicion in the Nursery

1 Term Newborn with Purple Rash at Birth

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CASE PRESENTATION

AUTHOR DISCLOSURE Drs Guthrie, Gillispie, Queliz-Pena, and Winners-Mendizabal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A male infant is born at 37 weeks and 6 days of gestation via planned cesarean delivery because of predicted macrosomia. The mother is a 23-year-old primigravida whose pregnancy had been complicated only by abnormal surveillance fetal ultrasonography findings concerning for fetal cardiac defect. Fetal echocardiography performed at approximately 32 weeks' gestation revealed biventricular hypertrophy and a dysplastic tricuspid valve with mild-to-moderate insufficiency. The pregnancy had been otherwise unremarkable. The mother denies use of drugs, illicit or prescription, alcohol, and tobacco during the pregnancy. Prenatal testing had shown the following results: human immunodeficiency virus, nonreactive; hepatitis B surface antigen, negative; rapid plasma reagin, nonreactive; and rubella, immune. Birthweight and length are 4.33 kg (97th percentile) and 51 cm (69th percentile), respectively. He is admitted to the NICU with a "blueberry-muffin" rash. Examination on admission is significant for macroglossia, right preauricular pit, multiple erythematous and purple nodules, purpura, petechiae, ankyloglossia, and thick umbilical cord.

Titers for cytomegalovirus (CMV), toxoplasma, and rubella and polymerase chain reaction testing for toxoplasma, parvovirus, CMV, and herpes simplex virus performed shortly after delivery are negative. Blood and cerebrospinal fluid cultures are also negative after 5 and 2 days, respectively. Abdominal ultrasonography excludes intra-abdominal tumors; however, the liver is at the upper end of normal at 6.1 cm. Head ultrasonography, computed tomography, and magnetic resonance imaging exclude calcifications as well as other abnormalities. Postnatal echocardiography reveals mild left ventricular dilation with borderline function, which resolves by 28 days after birth. Complete blood cell count at birth reveals the following: white blood cell count, $50 \times 10^3/\mu\text{L}$ ($50 \times 10^9/\text{L}$) with 63% monocytes, 15% leukocytes, 16% neutrophils, and 4% bands; hemoglobin, 16 g/dL (160 g/L); platelet count, $108 \times 10^3/\mu\text{L}$ ($108 \times 10^9/\text{L}$). Peripheral blood morphology is abnormal and a punch biopsy of a skin nodule gives a clue to the underlying condition. Immunophenotyping of the skin sample is positive for CD4, CD68, myeloperoxidase, CD45, lysozyme, and CD117. Microarray testing reveals an unbalanced 8;11 translocation with a terminal gain of chromosome 11 between bands p15.5 and p15.4 encompassing 8.4-Mb as well as 3.5-Mb terminal loss of chromosome 8 between bands p23.3 and p23.2. Confirmatory testing with fluorescence in situ hybridization testing confirms the presence of der(8)t(8;11)(p23.3;p15.4). Unfortunately, parental karyotyping has not yet been completed because of financial limitations.

CASE DISCUSSION

Diagnosis

Peripheral blood morphology was significant for marked myeloid left shift and absolute monocytosis. Punch biopsy of a nodule revealed myelomonocytic leukemic infiltrate involving the dermis and subcutis, thus confirming the diagnosis of congenital acute myeloid leukemia (AML). The genetic testing cited before as well as his numerous physical abnormalities allowed us to additionally diagnose him as having Beckwith-Wiedemann syndrome (BWS).

The neonate continued to develop leukemia cutis lesions after discharge, and a bone marrow aspiration revealed 24% blasts with flow cytology analysis significant for a distinct monoblast population classified as M5 in the French-American-British classification system based on staining and morphologic features. He has completed 2 courses of induction chemotherapy with cytarabine, etoposide, and daunorubicin for AML, resulting in zero percent minimal residual disease. He is now undergoing intensification chemotherapy with ara-C and etoposide.

The Condition

BWS is an overgrowth syndrome resulting from epigenetic abnormalities that disrupt genomic imprinting. It consists of a phenotypic expression that is variable and includes macrosomia, macroglossia, abdominal wall defects, hemihypertrophy, ear pits, visceromegaly, and neonatal hypoglycemia among many others. There are no official diagnostic criteria; however, a scheme by Weksberg et al is widely used: the presence of 3 major clinical signs or 2 major signs and 1 minor sign (Table). (1) Its incidence is approximately 1 in 13,700 births with equal female and male presentations. (2) The risk of developing embryonal tumors in patients with BWS is 4% to 21%, depending on which genetic anomaly is present, with nephroblastoma being the most frequent (43%). (1)

The high incidence of malignancy in BWS is related to genomic imprinting. Genomic imprinting is an epigenetic phenomenon in which expression of a subset of genes is parent-specific and controlled by imprinting control regions (ICRs). This subset of genes is clustered together in an imprinting domain and ICRs control the monoallelic expression of imprinted genes. Imprinted genes have an important role in human tissue growth and development. About 1% to 2% of BWS cases are a result of maternal translocation or paternal duplication. The current patient's genetic testing using subtelomeric probes revealed a duplication of 11p15. Unfortunately, the parental origin of this duplication is unknown because of financial limitations in parental karyotyping. Human 11p15 chromosome contains 2

imprinted domains important for growth: IGF2/H19 in the telomeric region and CDKN1C/KCNQ1OT1 in the centromeric region. ICR1 is methylated on the paternal allele prohibiting the attachment of CTCF and allowing H19 access to the promoters of IGF2. ICR1 is unmethylated on the maternal allele, preventing the activation of IGF2 and allowing the activation of H19. This results in the production of noncoding RNA; therefore, when the paternal allele is duplicated, IGF2 is overexpressed and H19 is downregulated. Rump et al concluded from their meta-analysis that the risk of cancer was the highest with a loss of imprinting at H19. (3) In our case, because it is unknown whether the duplication is maternal or paternal in origin, we are unable to assign a potential relationship between our patient's leukemia and H19 expression.

There have been few reports of leukemia in those with BWS. Our review of the literature revealed 4 such cases (Table): pre-B acute lymphoblastic leukemia (ALL), AML, T-cell ALL, and acute megakaryoblastic leukemia. (4)(5)(6)(7) To our knowledge, none of these cases included a congenital presentation. It has been proposed that the overexpression of insulinlike growth factor 2 (IGF2) is in part responsible for

TABLE. Generally Accepted Diagnostic Criteria for Beckwith-Wiedemann Syndrome

Major Criteria	
Abdominal wall defects	Anterior ear lobe crease/pit
Macroglossia	Embryonal tumor
Hemihypertrophy	Adrenal fetal cortex cytomegaly
Macrosomia	Renal abnormalities
Visceromegaly	Cleft palate
Positive family history of Beckwith-Wiedemann syndrome	
Minor Criteria	
Pregnancy related findings like polyhydramnios, placentomegaly, thickened umbilical cord	Cardiac anomalies, cardiomegaly, cardiomyopathy
Neonatal hypoglycemia	Characteristic facies
Nevus flammeus	Diastasis recti Advanced bone age

the overgrowth of tissue in patients with this syndrome. IGF is expressed on T and B cells, and it has been proposed that IGF is linked to the pathogenesis of leukemias. (5)

The loss of imprinting at *H19* that results in overexpression of *IGF2* suggests that this overexpression may contribute to carcinogenesis. The endocrine hormone *IGF2* induces autocrine expression in AML cells and increases their proliferation. In addition, *IGFBP2*, a regulatory binding protein, has been found to be aberrantly expressed in AML cells leading to higher-grade tumors and chemoresistance. (8)

Treatment

Treatment is largely supportive and surveillance. Surgical correction may be required for omphalocele, leg length discrepancy, or facial asymmetry. Special assistance with feeding may be required because of macroglossia or cleft palate. Hypoglycemia is a risk most likely because of hyperinsulinemia secondary to islet cell hyperplasia, so this should be monitored while in the newborn nursery. Patients with BWS should be monitored for tumors, including renal, liver, pancreatic, and adrenal, using ultrasonography every 3 months until age 8 years. Screening should also include the measurement of α -fetoprotein every 2 to 3 months during the first 4 years to detect hepatoblastoma. Annual renal ultrasonography is then performed from age 8 years to adolescence to survey for renal abnormalities. After leaving the nursery, treatment is often needed for speech difficulty and developmental delay.

Lessons for the Clinician

- A purpuric rash in the neonate has a wide differential diagnosis including malignancy.
- Beckwith-Wiedemann syndrome is highly associated with tumors and as such close surveillance is required.

- Although embryonal tumors are most common, leukemias in this population have been documented and should be kept in the differential for possibly affected patients.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology, molecular phenotype, and clinical manifestations of disorders associated with genetic imprinting, such as Prader-Willi syndrome.
- Know the clinical and laboratory features of congenital leukemia.

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Index of Suspicion in the Nursery

3 The Hypothermic Newborn

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PRESENTATION

A 2-day-old male infant born at 38 weeks to a gravida 1, para 1 woman is brought to the emergency department secondary to concerns for hypothermia, poor feeding, and decreased urine output. Prenatal laboratory results are unremarkable, with the exception of group B *Streptococcus* colonization that was adequately treated with penicillin prophylaxis before delivery. The delivery course was notable for thick meconium for which the infant underwent intubation and suctioning with subsequent extubation. The infant's Apgar scores were 4 and 9 at 1 and 5 minutes, respectively. In the nursery, the infant was noted to be breastfeeding well and had passed stools and voided appropriately. He was discharged on day 2 after birth.

After discharge, the parents contacted the infant's physician to report decreased interest in feeding, decreased activity, and low rectal temperature of 93.9°F (34.4°C). The family was instructed to take the infant to the emergency department for further evaluation and treatment. On arrival at the emergency department, the infant was noted to have a temperature of 96.9°F (36.1°C) and to be listless, and was thus taken to a resuscitation bay. Initial physical examination showed an ill-appearing infant with tacky mucous membranes and an exaggerated Moro reflex. He was given a 10-mL/kg normal saline bolus and a 15-mL/kg normal saline bolus.

Initial laboratory findings include the following: white blood cells 22,000/ μ L (22×10^9 /L); hemoglobin 13.3 g/dL (133 g/L); hematocrit 36.5%; platelet count, 565×10^3 / μ L (565×10^9 /L); neutrophils 80%; bands 1%; lymphocytes 12%; monocytes 5%; sodium 154 mEq/L (154 mmol/L); potassium 5.1 mEq/L (5.1 mmol/L); chloride 115 mEq/L (115 mmol/L); bicarbonate 20 mEq/L (20 mmol/L); blood urea nitrogen 6 mg/dL (2.14 mmol/L); creatinine 1.4 mg/dL (123.7 μ mol/L); and glucose 102 mg/dL (5.6 mmol/L). These tests were interpreted as leukocytosis with neutrophilic predominance but without a significant proportion of immature cells, hypernatremia, and an anion-gap metabolic acidosis. Cerebrospinal fluid (CSF) and urine specimens were collected and results were as follows: CSF white blood cells 7,000/ μ L (7×10^9 /L); CSF red blood cells 149×10^6 / μ L (149×10^{12} /L); CSF glucose 63 mg/dL (3.5 mmol/L); CSF protein 96 mg/dL (960 mg/L); urine pH 6.0; urine leukocyte esterase negative; urine nitrite negative; urine bacteria many; urine white blood cells negative. Neonatology was consulted at this point. Initiation of ampicillin and gentamicin and admission to the special care nursery were recommended.

The infant was subsequently transferred to the special care nursery where he was noted to have a distended abdomen; an anteroposterior abdominal radiograph showed intraluminal distention but no free air, pneumatosis coli, or

AUTHOR DISCLOSURE Drs Erickson and Schrier Vergano have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

portal venous gas. He subsequently became apneic and underwent intubation and was transferred to the NICU for further management. On arrival at the NICU, umbilical arterial and venous lines were placed, through which intravenous fluids were administered at a rate of 140 mL/kg per day and a Foley catheter was placed to monitor urine output. Given the elevated creatinine level, gentamicin was discontinued and cefotaxime was started. The infant was also started on oxacillin treatment at this point to broaden empiric coverage. A capillary blood gas, ammonia level, repeat hemoglobin/hematocrit, and coagulopathy panel measurements were obtained. The results of these tests were as follows: blood pH 7.07; P_{CO_2} 71 mm Hg (9.5 kPa); base excess -9; ammonia more than 1,400 μ g/dL ($>1,000 \mu$ mol/L), hemoglobin 9.9 g/dL (99 g/L); hematocrit 29%; prothrombin time 22.4 seconds; partial thromboplastin time 46.6 seconds; fibrinogen level 131.2 mg/dL (3.8 μ mol/L). These results were interpreted as a likely metabolic derangement with concomitant coagulopathy and respiratory acidosis. The infant was given 15 mL/kg of packed red blood cells and 10 mL/kg of fresh frozen plasma; ventilator settings were adjusted to increase ventilation; and medical genetics was consulted.

Based on genetics recommendations, the infant was started on the intravenous nitrogen scavenger sodium phenylacetate and sodium benzoate and arginine infusion. The infant continued to undergo serial ammonia and lactate measurements; additional metabolic laboratory studies were performed, including plasma amino acids, urine organic acids, acylcarnitine profile, and urine orotic acid. Despite the nitrogen scavenging medications, the infant continued to have ammonia levels greater than 1,358 μ g/dL (970 μ mol/L) for the remainder of the morning of admission. An internal jugular vein central venous line was placed in preparation for dialysis. After this, the infant's ammonia level began to show a downward trend to 393 μ g/dL (281 μ mol/L), continued to decrease to 93 μ g/dL (67 μ mol/L) in the following 24 hours, and normalized on the following day.

DIAGNOSIS

Plasma amino acid and urine organic acid results were obtained within 48 hours, and were remarkable for increased citrulline, excretion of argininosuccinate anhydrides, and positive urine orotic acid. These results suggested a diagnosis of argininosuccinate (ASA) lyase deficiency. Low-protein total parenteral nutrition was started on hospital day 3 and nasogastric feeds were initiated on day 6 of hospitalization with a mixture of amino acid-restricted

formula and breast milk, given the presumptive diagnosis of ASA lyase deficiency. Genetic testing demonstrated that the infant was heterozygous for 2 pathogenic variants of the *ASL* gene, confirming the diagnosis. The infant's newborn screening performed at 11 days after birth showed an elevated citrulline level. The infant continued to improve and was taken off all support with excellent oral feeds. He was subsequently discharged from the hospital with a nasogastric tube in place for medications and to continue with arginine, sodium benzoate, and sodium phenylbutyrate. He continued to receive close follow-up by his pediatrician and medical genetics specialist and ultimately received an orthotopic liver transplant at 8 months of age. He continues to thrive and meet his developmental milestones.

THE CONDITION

ASA lyase deficiency is an autosomal recessive condition with an estimated incidence of approximately 1 in 70,000 live births. (1) ASA lyase is the enzyme involved in the urea cycle, which breaks down ASA to produce fumarate and arginine. The deficiency or lack of this enzyme causes buildup of citrulline, the compound detected on newborn screening for identification of ASA lyase deficiency. Elevated citrulline can also be seen in citrullinemia, another urea cycle disorder, as well as pyruvate dehydrogenase deficiency. As such, plasma amino acids must be checked for levels of ASA and its anhydrides to confirm the diagnosis of ASA lyase deficiency. Infants with ASA lyase deficiency (or other urea cycle disorders) will typically present with feeding difficulties and hypothermia after an initial period of wellness. As ammonia levels climb, however, the infant will have increasing central nervous system signs because of cerebral edema, and may include respiratory alkalosis, lethargy, seizures, and coma. Unique to ASA lyase deficiency are the findings of systemic hypertension and trichorrhexis nodosa (areas of partial alopecia with brittle hair). (2)

It is typically treated in the acute phase with nitrogen scavenger therapy, arginine supplementation, and a protein-free diet while still providing adequate glucose to prevent catabolism. If the clinician is unable to normalize the serum ammonia levels, hemodialysis must be considered. Over the long term these patients do benefit from orthotopic liver transplantation because this will prevent further metabolic crises.

Lessons for the Clinician

- Clinicians should have a high index of suspicion for hyperammonemia when infants present with hypothermia,

tachypnea, poor feeding, and lethargy between 2 and 7 days of age.

- Once the diagnosis of hyperammonemia is made, prompt therapy with arginine, nitrogen scavenger therapy, and prevention of catabolism, while restricting protein intake, is crucial to reduce the ammonia levels and potentially prevent the impact on neurocognition.
- An elevation of citrulline on newborn screening is suggestive of argininosuccinate lyase deficiency, citrullinemia, or pyruvate carboxylase deficiency. To clarify the diagnosis from this point, a serum amino acid panel is necessary.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.

- Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants.
- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.

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Index of Suspicion in the Nursery

1 The Icteric Infant 12 Hours After Birth

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AUTHOR DISCLOSURE Drs Langston, Upadhyay, and Gibson have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

The nursery notifies the medical team of a term female infant born at 40 weeks' gestation via vacuum-assisted vaginal delivery. Maternal prenatal care was unremarkable. Prenatal laboratory findings are significant for maternal rubella non-immune status and maternal blood type B positive, antibody negative. Events surrounding the delivery are notable for category II tracings on fetal monitor, 3+ meconium, and 1 detachment ("pop-off") during vacuum application. Apgar scores are 9 and 9 at 1 and 5 minutes, respectively.

At approximately 12 hours after birth, the medical team is notified of a transcutaneous bilirubin measurement that is outside the normal clinical range. The infant appears jaundiced on physical examination. The total serum bilirubin concentration is 20.6 mg/dL (1821 μ mol/L). The neonate is transferred to the NICU for close observation and initiation of triple phototherapy.

DISCUSSION

Diagnosis and Hospital Course

Hyperbilirubinemia observed in the first 24 hours after birth is considered pathologic, or non-physiologic jaundice, and warrants urgent evaluation. Blood dyscrasias and hemolysis should be suspected in cases of severe hyperbilirubinemia and should prompt laboratory evaluation. A specific differential diagnosis should include red blood cell (RBC) membrane defects such as spherocytosis and elliptocytosis, thalassemias, minor blood group antibodies, and enzyme defects such as glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency.

Phototherapy was initiated at approximately 13 hours after birth once serum bilirubin levels were obtained. After 2 hours of receiving triple phototherapy, the unconjugated serum bilirubin concentration remained stable at 20.8 mg/dL (1838 μ mol/L). The lactate dehydrogenase level was elevated at 1,831 U/L (30.58 μ kat/L) and haptoglobin was low, prompting concern for a hemolytic process. The hemoglobin and hematocrit were observed to be 9.6 g/dL (96 g/L) and 29.3% (0.30), respectively. An exchange transfusion was initiated with 400-mL admixture of RBC/fresh frozen plasma (which was 85% of the total blood volume) with subsequent administration of intravenous immunoglobulin. Head ultrasonography found no evidence of hemorrhage. Hematology was consulted to further characterize the hemolytic process. A peripheral smear showed "normocytic anemia with numerous nucleated RBCs. RBC anisopoikilocytosis includes

polychromasia, microspherocytes (1–2 per high-power field), scattered fragments, and increased numerous nucleated RBCs. Left-shifted granulocytes with rare blasts are seen, probably under stress conditions.” A mixing study between mother and neonate did not demonstrate hemolysis, and the result of G6PD deficiency testing was negative. Due to inconclusive laboratory findings, genetic testing was performed using next-generation sequencing, which identified a 2-gene deletion for the *PKLR* gene. This confirmed pyruvate kinase deficiency.

Clinical Features

Pyruvate kinase deficiency is one of the most common causes of hereditary nonspherocytic chronic hemolytic anemia. It is inherited in an autosomal recessive manner and results in mutation of the *PKLR* gene, which codes for the pyruvate kinase enzyme in RBCs and the liver. Affected individuals have either homozygous mutations or are compound heterozygotes. Defects in pyruvate kinase cause abnormalities in glycolysis, with subsequent decreased production of adenosine triphosphate (ATP), the cell’s primary source of energy. With decreased ATP, the RBC is deemed nonviable and destroyed by the spleen. Due to this increased RBC destruction, the patient is at risk for severe anemia with splenomegaly. The phenotype is variable and can range from mild to severe. The mild phenotype tends to present with neonatal jaundice and rarely requires transfusion, whereas severe phenotypes require exchange blood transfusions and carry a high risk of death. Severe phenotypes appear to be associated with disruptive mutations or missense mutations and result in disease onset in the neonatal period.

The Condition

Pyruvate kinase deficiency is diagnosed via genetic sequencing and has a wide molecular genotype with more than 200 mutations identified. Severe cases of pyruvate kinase deficiency present in the neonatal period, whereas mild cases may not present until adulthood. However, the correlation between disease severity and active enzyme level is poor. Affected neonates may die in utero from nonimmune hydrops or present with severe jaundice in the first 24 hours after birth requiring exchange transfusion. In mild cases, children and adults present with characteristic findings of chronic hemolytic anemias such as icterus and splenomegaly. Treatment for pyruvate kinase deficiency remains supportive, including frequent blood transfusions and splenectomy. Studies are currently investigating gene

therapy to correct the mutation in the *PKLR* gene versus administration of an agonist to pyruvate kinase. Regardless, diagnosis of pyruvate kinase deficiency is critical to prevent morbidity and mortality of the neonate as well as to provide appropriate long-term management.

Lessons for the Clinician

- A neonate with jaundice in the first 12 hours after birth should be evaluated urgently because it is concerning for a hemolytic process, such as pyruvate kinase deficiency.
- Pyruvate kinase deficiency is a diagnosis confirmed on genetic sequencing with a variety of genotypic differences.
- Treatment of pyruvate kinase deficiency is supportive, but new investigations are considering gene therapy to correct the mutation.

American Board of Pediatrics Perinatal-Neonatal Content Specifications

- Know the differential diagnosis and evaluation of infants with indirect hyperbilirubinemia.
- Know the etiology and pathophysiology of hemolytic anemias in the neonate.

Suggested Readings

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Case 1: The Icteric Infant 12 Hours After Birth
Seth J. Langston, Shivani Upadhyay and Leena Caroline Gibson
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Index of Suspicion in the Nursery

1 The Impact of Methylergometrin Maleate Toxicity on Neonates

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AUTHOR DISCLOSURE Drs Badawy, Darwich, and Aqeel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A full-term male neonate of 2.6 kg birthweight is born via a spontaneous vaginal delivery to a mother who denies any unfavorable obstetric or medical history. The delivery occurs at a peripheral hospital without any labor challenges. Approximately 20 minutes after delivery, the neonate develops central cyanosis and respiratory distress, for which he receives respiratory support in the form of oxygen through a nasal cannula. A decision is made to refer him to a tertiary NICU.

On arrival at the NICU, lung auscultation reveals bilateral equal air entry, no adventitious sounds, subcostal and intercostal recessions, a respiratory rate of 70 breaths/min, and oxygen saturation above 95% in room air. Normal first and second heart sounds are heard, plus a systolic 3/6 murmur over the left upper sternal border; the heart rate is 155 beats/min, mean blood pressure is 60 mm Hg (75/50 mm Hg), and echocardiography shows an insignificant patent ductus arteriosus and small atrial septal defect secundum.

The abdomen is soft and lax with no organomegaly detected. Neurologic examination shows lethargy, hypotonia, hyporeflexia of the deep tendon reflexes, and diminished primitive reflexes; the pupils are 2 mm in diameter with sluggish reaction to light bilaterally. Cranial ultrasonography depicts partially effaced ventricles as well as cerebrospinal fluid spaces denoting the possibility of brain edema (Fig 1); electroencephalographic monitoring is normal.

Electrocardiography (ECG) shows a sinus rhythm, normal rate, right axis deviation, initial QTc of 469 milliseconds, which increased to 532 milliseconds by the fourth day, then back to 500 milliseconds on the next day (it is interpreted as a significant prolonged QT interval) (Fig 2).

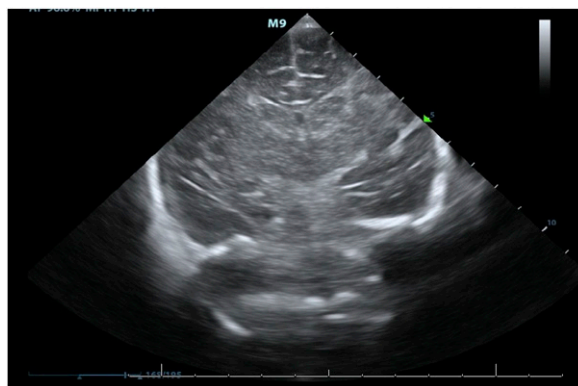


Figure 1. Cranial ultrasonographic scan showing a partially effaced ventricle as well as cerebrospinal fluid spaces that denote the possibility of brain edema.

Rate 151 . Age not entered, assumed to be 0 years old for purpose of ECG interpretation
 Sinus tachycardia.....rate> 99
 PR 136 . Consider right atrial enlargement.....P >0.24mV limb lead
 QRSD 61 . Posterior infarct, acute (ICx).....ST<-0.1 V1-V3 or ST>.05 V7-V9
 QT 335 . Prolonged QT interval.....QTc >500ms
 QTc 532

--AXIS--
 P 79
 QRS 136
 T 12

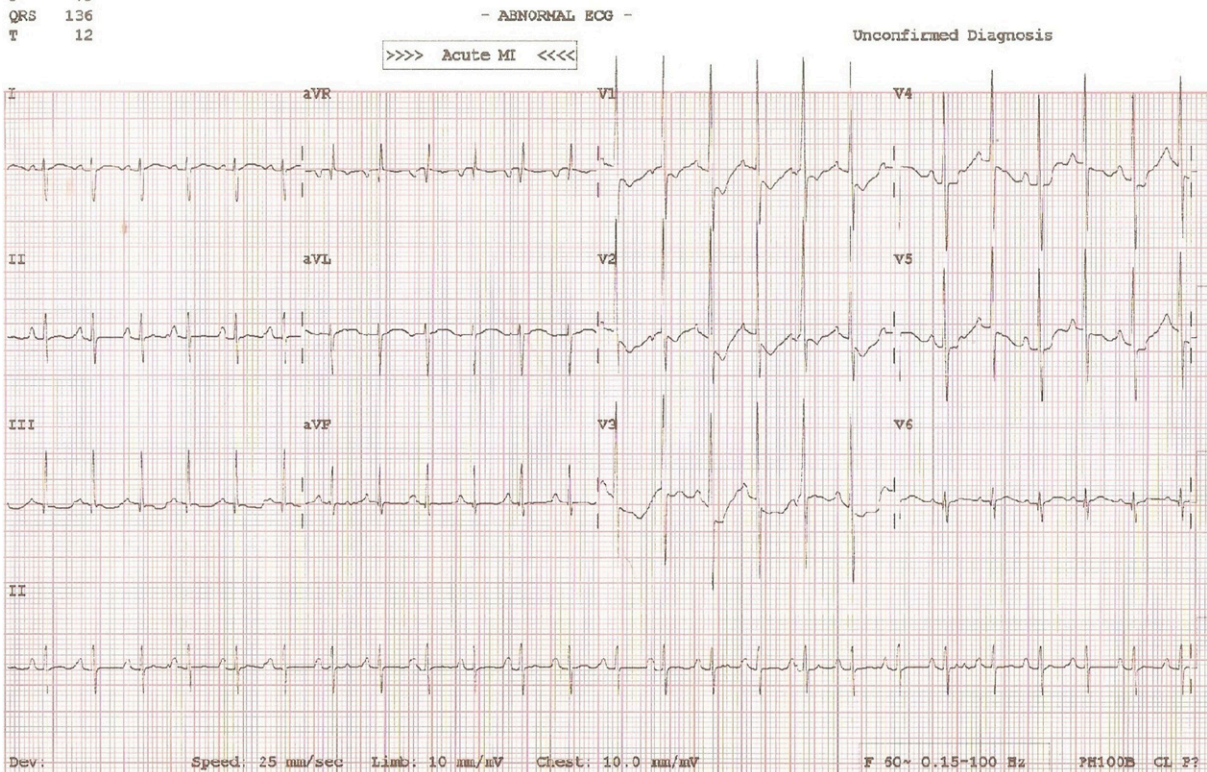


Figure 2. Electrocardiography using 12 leads on the fourth day identifies sinus rhythm, normal rate, right axis deviation, and QTc of 532 milliseconds (which is interpreted as a significant prolonged QT interval).

Although laboratory findings are normal, the only abnormality identified is an elevated creatinine phosphokinase (CPK) level, which reaches 2,980 U/L then gradually declines to 249 U/L before discharge.

DISCUSSION

Differential Diagnosis

The list of differential diagnoses is long because the clinical picture is nonspecific; however, sepsis and birth asphyxia were considered on the top of the list.

Actual Diagnosis

Methylergometrin maleate intoxication as a medication error.

The Condition

Intramuscular vitamin K (phytomenadione) is usually prescribed to neonates as prophylaxis for hemorrhagic disease of the newborn. Although it is rare to misread the label of a

vitamin K ampule, it occurs occasionally, as in the current case. The neonate was injected with 0.04 mg (0.015 mg/kg) intramuscular methylergometrin maleate, which was stored in the refrigerator instead of vitamin K, which commonly is stored on shelves outside. Even though this is difficult to discover, the assigned nurse honestly admitted her error.

Methylergometrin maleate (an ergot derivative) is used by obstetricians to reduce the possibility of postpartum hemorrhage through its action on the uterine smooth muscle and its vasculature.

Neonatal methylergometrin toxicity has a variable non-specific presentation that could mimic other neonatal disorders, (1) therefore, it might be missed easily.

Morbidity and even mortality due to neonatal ergot poisoning are documented. (2)

Respiratory compromise is considered the most frequent presentation, ranging from distress and mild cyanosis, which needs minimal support, to apnea and respiratory failure, which needs ventilatory support. Some clinicians

use naloxone as well as nitroprusside infusions as an effective medication to counter the effect of methylergometrin maleate toxicity (2)(3)(4)(5); thus, admission to a tertiary NICU unit is paramount.

Encephalopathy has been observed frequently in the cases reported since the 1960s. Lethargy alternates with agitation, and seizures are noticed as well. (1)(2)(5) Although we did not find any evidence of radiologic brain changes throughout the reviewed cases, brain edema changes were captured on initial head ultrasonography in our patient.

Cardiovascular system and ECG monitoring are not well appreciated, to our knowledge; however, we found that a prolongation of QT interval could be due to methylergometrin intoxication (needs thorough scrutiny).

CPK is markedly increased initially then declines along with clinical improvement; however, CPK level is not well elaborated in the other case studies.

Feeding intolerance, peripheral circulation abnormalities, oliguria, and death have been reported, (1)(2)(3)(4)(6) but these hazards were not noticed in the current case.

Clinical manifestations in our neonate were mild compared with other reported cases, which confirms our belief that these manifestations may be dose dependent. This is because in other cases, patients who received doses ranging from 0.1 mg to 0.5 mg required more aggressive support. (2)(5)(7) A literature review shows that age and route of administration could play a significant role in the variations in clinical presentation among patients. (3)(6)

Management

Supportive care and close observation as well as monitoring of vital signs are adequate during admission.

Patient Course

The patient's overall vital signs were maintained throughout his NICU stay (6 days). Feeding was started after 24 hours, initially by orogastric tube for 2 days then by breastfeeding, and he did not need any respiratory support. Tone, power, pupils' reactivity to light, and reflexes began to improve after the first day of admission, and the neonate recovered completely after 72 hours of age. Brain magnetic resonance imaging findings before discharge were normal.

Lessons for the Clinician

- Medication errors are considered one of the leading causes of morbidity and mortality, therefore notifications

about their occurrence are essential for tackling the hazards. These errors could be minimized by a well-written protocol, raising the awareness of medication safety and proper administration, and clarifying policy, as well as adhering to senior staff supervision.

- Respiratory compromise and encephalopathy are by far the most frequent manifestations of methylergometrin maleate toxicity. The aggressiveness of medical support is believed to be directly proportional to the dose given.
- Electrocardiographic changes in the form of prolonged QT intervals as well as elevated creatinine phosphokinase might be considered as a sign of methylergometrin maleate intoxication.
- Admission to NICU is guaranteed to a patient who experiences methylergometrin maleate toxicity.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- For therapeutic drugs commonly used in the neonate (eg, opiates, methylxanthines, barbiturates, etc), know indications for their use, clinical effects, side effects, and toxicity.

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Index of Suspicion in the Nursery

1 The Inconsolable Infant in the NICU

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AUTHOR DISCLOSURE Drs Kurada and Joseph have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is born at 30 weeks of gestation via vaginal delivery due to imminent labor. The infant receives 1 dose of surfactant in the delivery room for respiratory distress, after which she is transferred to the NICU for further care.

Anthropometric measurements at birth are: weight, 595 g; length, 29 cm; and head circumference, 23.5 cm. Birthweight, length, and head circumference are below the 5th percentile for the corresponding gestational age. Wide forehead, 2 natal teeth on the mandibular ridge, hypertonia of all extremities, grade 2 systolic murmur, and bilateral inguinal hernias are noted on examination. Specific immunoglobulin M values for toxoplasma, rubella and cytomegalovirus virus are negative. Head ultrasonography reveals no calcifications or other abnormalities. Skeletal survey shows no signs of perichondritis. Retinal examination to check for signs of chorioretinal inflammation that could point toward a particular TORCH (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes) infection are negative. Peripheral pulmonary arteries are found to be mildly hypoplastic on echocardiography, which is conducted as part of an evaluation for an audible murmur. Ultrasound imaging of kidneys and bladder reveals no anatomic abnormalities.

The patient undergoes elective extubation 24 hours after birth. She makes a transition to room air within 72 hours after birth. After extubation, she has a high-pitched cry, and a hyperactive anxious disposition that requires much attention from nursing staff and is inconsolable. She has abnormally long cry times that are 8 to 12 hours a day. Thyroid profile indicates euthyroid status. Urine toxicology screening result is negative. Electroencephalography is age appropriate. Magnetic resonance imaging of the brain shows no anatomic abnormalities. Neonatal pain score is persistently high requiring intervention. Auditory brainstem response shows unilateral sensorineural hearing deficit on the right side and normal conduction on the left side.

Frequent abdominal distention hinders the advancement of enteral feeds. Contrast studies do not reveal any anatomic obstruction and enteral feeds are continued through a nasojunal tube. Most of her nutrition is given parenterally because of repeated failures in oral feeding attempts. Swallow evaluation shows complete lack of coordination of swallow and suck, along with failure to create suction pressure with a good seal around the nipple, thus causing leakage of oral feeds from the side of her mouth. Catch-up growth is not seen. Percutaneous gastrostomy tube placement restored enteral feeds, which assist in appropriate weight gain.

Repeat echocardiography at 4 weeks reveals mildly hypoplastic pulmonary trunks and supravulvar pulmonary stenosis. Balloon dilation of the pulmonary valve is performed to reduce the pressure gradient across the stenosis.

Karyotype analysis reveals 46,XX and chromosomal microarray confirms the diagnosis.

DISCUSSION

Diagnosis

Cri-du-chat could be considered as part of the differential diagnosis because of the high-pitched cry and microcephaly. The differential diagnosis includes Williams syndrome (WS) because of the pulmonary stenosis, unilateral sensorineural hearing loss, and short stature.

The microarray revealed 7q11.23 microdeletion encompassing the elastin *ELN* gene, which is characteristic of WS. WS is now recognized to be a multisystem genomic disorder caused by a homozygous microdeletion of chromosome 7q11.23. The deleted portion of the WS gene includes the *ELN* gene, which codes for structural protein elastin.

All of the following features point toward a condition with a genetic etiology: feeding problem, anxious disposition, inconsolable crying during hospital stay, bilateral inguinal hernia, sensorineural hearing loss, decreased gut motility, lack of suck-swallow coordination for oral feeds requiring gastrostomy to advance enteral feeds, peripheral pulmonary stenosis with supravalvular pulmonary stenosis requiring balloon dilation, and short stature.

The Condition

The incidence of WS is 1 in 10,000 live births. The facial features are described as “elfin facies” with a broad forehead and a wide mouth. The incidence of auditory problems, including hypersensitivity and sensorineural hearing loss, is 50% to 90%. Malocclusion and microdontia are the reported dental malformations with a high incidence of 85% to 95%. Early postnatal teeth is not a well-known entity and not commonly seen in WS.

Twenty-five percent of patients with supravalvular aortic stenosis have WS, which makes it a very specific finding. Pulmonary arterial stenosis is the second most common cardiovascular abnormality seen in WS. Supravalvular pulmonary stenosis, although rare, is seen in affected infants. Other major blood vessels such as the renal arteries have also been reported to be affected. Hypertension is another problem that would be evident in adolescents.

Feeding difficulties seen in most affected children becomes the most common gastrointestinal manifestation of the WS. Constipation is the second most common gastrointestinal manifestation.

Lax skin and hernias that are inguinal or umbilical in location are commonly seen. Calcium metabolism issues, hypothyroidism, and type 1 diabetes mellitus are also seen rarely.

Most affected children have joint hypermobility and contractures that result in an awkward gait. Central hypotonia and peripheral hypertonia with hyperactive deep tendon are found in children with WS.

Cognition is affected almost universally. Developmental delay is expected in 95% of the affected children. Affected children have defects in the visuospatial constructive cognition. Attention-deficit/hyperactivity disorder and generalized anxiety disorder are seen in older children. We believe this anxiety manifested, even at an early age, as inconsolable crying in our patient. Overfriendliness, a gregarious personality, and an empathetic nature are also commonly observed.

Management

The American Academy of Pediatrics published guidelines in 2001 for the evaluation and primary care of children with WS. Special considerations were mentioned and categorized by age from birth to adolescence. Baseline evaluation and integration of communication among the cardiologist, primary care physician, nephrologist, child psychiatrist, and therapist is emphasized. Pediatric orthopedics should be involved from early childhood for frequent surveillance for kyphosis, scoliosis, and early detection and prevention of problems that lead to awkward gait. Most common cause for mortality after the third decade of life is cardiovascular in origin.

Lessons for the Clinician

- A neonate who is symmetrically small for gestational age with no findings of in utero TORCH (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes) infections should be evaluated for genetic causes of the condition.
- Neurologic examination of growing premature infants including disposition should be done elaborately on a regular basis to keep a close watch on interval changes.
- Supravalvular aortic and pulmonary arterial stenosis is strongly associated with Williams syndrome, which can be confirmed by 7q11.23 sequencing.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize clinical manifestations and laboratory methods for diagnosis of the microdeletion syndromes.

Suggested Readings

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Index of Suspicion in the Nursery

2 The Inconsolable Newborn

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AUTHOR DISCLOSURE Dr Migliore has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-day-old male newborn of 39 weeks' gestational age was brought to the emergency department (ED) with a complaint of "shaking of upper and lower extremities and fussiness" since birth. After the initial episode at home, he presented to the primary care physician with 2 more shaking episodes that occurred in clusters of 3 minutes described as jerking of both upper and lower extremities with occasional head jerking. The shaking is not associated with eye rolling or with feeds. Concerned about possible seizures, the physician recommended admission to the NICU for further evaluation. The patient did not have a fever, rash, or upper respiratory tract infection symptoms. There was 1 episode of nonbilious, nonbloody vomiting on the day of presentation. He had 10 to 11 wet diapers per day and 8 to 9 stools per day. There was no change in alertness and energy.

He is a term infant, born by repeat cesarean delivery to a 32-year-old gravida 5-3-0-2-3 mother, who had received adequate prenatal care. The pregnancy was pertinent for a history of *Escherichia coli*-positive urinary tract infection at 24 weeks' gestation and a medical history that included a *Chlamydia* infection, which had been diagnosed and treated before this pregnancy. Fetal movement and cervical examination findings were normal. She was group B *Streptococcus* negative, rapid plasma reagin test nonreactive, rubella immune, and hepatitis B surface antigen negative. Maternal urinary drug screening was not performed at the birth hospital.

On arrival at the ED, the patient was afebrile, with a temperature of 99.6°F (37.6°C), heart rate 148 beats/min, respiratory rate 48 breaths/min, and oxygen saturation of 100% on room air. A shaking episode noted in the ED was described as shaking of the arms and legs without eye deviation or foaming at the mouth. It lasted a couple of seconds. Electrolytes, complete blood cell count, and urinalysis findings were within normal limits. Laboratory findings were as follows:

- Sodium, 132 mEq/L [132 mmol/L]
- Potassium, 7 mEq/L [7 mmol/L] with moderate hemolysis
- Chloride, 100 mEq/L [100 mmol/L]
- Bicarbonate, 18 mEq/L [18 mmol/L]
- Serum urea nitrogen, 8 mg/dL [2.8 mmol/L]
- Calcium, 9.5 mg/dL [2.4 mmol/L]
- Magnesium, 2 mEq/L [1 mmol/L]
- Phosphorus, 7.1 mg/dL [2.3 mmol/L]
- White blood cells, 11,200/ μ L [11.2×10^9 /L]
- Neutrophils, 44%
- Lymphocytes, 40%
- Monocytes, 15%
- Eosinophils, 1%
- Hemoglobin, 15.6 g/dL (156 g/L)

- Hematocrit, 45.2%
- Platelets, $460 \times 10^3/\mu\text{L}$ [$460 \times 10^9/\text{L}$])

Blood culture, polymerase chain reaction for herpes simplex virus (HSV PCR), C-reactive protein of less than 2 mg/L (19 nmol/L), and ammonia 83 $\mu\text{g/dL}$ (59 $\mu\text{mol/L}$) were normal for age.

On arrival at the NICU, electrocardiography showed normal sinus rhythm. Cerebrospinal fluid studies showed glucose of 64 mg/dL (3.5 mmol/L), protein 8.3 g/dL (83 g/L), nucleated cells 2/ μL (83% monocytes, 17% lymphocytes), red blood cells 0/ μL ; culture, HSV PCR, enterovirus, and virus cultures were all found to be negative. The neonate was fussy and occasionally consoled by feeding. He was fed on demand, and had an intake of 60 to 120 mL every 3 hours. Finnegan scores recorded were 15 to 21.

Diagnosis

On inquiry, the parent denied the habitual use of drugs or other medications during pregnancy, and admitted to smoking 1 pack of cigarettes per day during the course of her pregnancy. She also revealed that she had been drinking about 2 to 4 cups of Arabic tea, 2 to 4 cups of coffee, and 2 caffeinated energy drinks per day during her third trimester which makes for a total caffeine intake of up to 792 mg/day. The neonate's caffeine level was found to be 4. Caffeine withdrawal was suspected, and the infant was given a loading dose of caffeine at 5 mg/kg. He was then started on maintenance caffeine therapy at 5 mg/kg divided twice daily the following day. The infant demonstrated an immediate clinical response, with no further agitation and lower Finnegan scores (3-10) after the first dose. The caffeine dose was tapered every other day by 1 mg/kg and given twice daily, until day 7, to daily dosing. Finnegan scores were at 0 to 2 before discontinuation.

It is important to formulate a differential diagnosis in a newborn who presents to the ED with a history of shaking or abnormal movements of extremities. The following etiologic factors should be considered:

1. Sepsis versus meningitis
2. Seizure activity
3. Hypoxic-ischemic encephalopathy
4. Intracranial hemorrhage versus trauma
5. Cerebral anomaly
6. Subdural effusion
7. Metabolic disorder: Hypocalcemia, hypoglycemia, hypo and hypernatremia as well as water intoxication, that is, proper mixing of formula, etc.
8. Cerebral infarction
9. Pyridoxine dependence
10. Neonatal abstinence syndrome: From narcotic drugs, antipsychotics, or caffeine

The Condition

Caffeine is a methylxanthine that is available in coffee (85–110 mg per cup), tea (50 mg per cup), cola, cocoa, and energy drinks such as “Monster” (Monster Beverage Corp, Corona, CA), which contain 86 mg caffeine per serving. The primary metabolite of caffeine is paraxanthine which can cross the placental barrier, allowing exposure of the fetus to all maternally consumed caffeine. Caffeine and its metabolites can be found in amniotic fluid, uterine secretions, fetal tissues, cord blood, blastocyst, and breast milk as early as 1 hour after consumption. Aaronson and Macnee concluded in 1989 that maternal caffeine consumption is an accurate indication of fetal caffeine exposure. Furthermore, neonates excrete about 85% of it unchanged in the urine, with a half-life of 4 days. Adult patterns of caffeine metabolism do not occur until about 7 to 9 months of age. Case report from 1988 described infants with pallor of the skin and lower extremity as well as tonic movements of the legs with associated vomiting; the symptoms resolved 6 days later without intervention in a mother who had ingested about 450 to 535 mg of caffeine per day for the last 4 to 5 months of her pregnancy. Another important factor to consider is the tripling of the half-life of caffeine during the third trimester of pregnancy, which causes even higher blood levels of caffeine, and subsequently, an increased effect on the fetus.

Lessons for the Clinician

There currently is no guideline or protocol in place regarding caffeine withdrawal in the neonate. In 1988, McGowan et al described 3 cases of neonatal caffeine withdrawal, and suggest that it is important to take a maternal dietary history when symptoms such as tremulousness and nonbilious vomiting are recognized. A wide range of symptoms can be seen in these patients, however, ranging from an inconsolable neonate to what some would describe as seizurelike activity. It is important to not only obtain a good dietary history, but also ask specifically about caffeine consumption, because many would not consider this part of their diet.

American Board of Pediatrics Neonatal—Perinatal Content Specification

- Know the drugs associated with neonatal abstinence syndromes including maternal substance abuse and those administered in the NICU

Suggested Readings

- Aaronson LS, Macnee CL. Tobacco, alcohol, and caffeine use during pregnancy. *J Obstet Gynecol Neonatal Nurs*. 1989;18(4):279–287
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Case 2: The Inconsolable Newborn

Marina Migliore

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DOI: 10.1542/neo.18-1-e67

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Index of Suspicion in the Nursery

2 The Well-Appearing Cyanotic Infant

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AUTHOR DISCLOSURE Drs Krick, Kironde, and Hendrickson have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term male infant is born via spontaneous vaginal delivery at 40 2/7 weeks' gestational age to a gravida 2 para 2 mother. Her pregnancy was complicated by maternal tobacco use and inadequately treated group B *Streptococcus* colonization. The infant is vigorous at birth with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. The infant has growth parameters appropriate for gestational age and examination in the delivery room reveals bilateral clubfeet, but is otherwise normal.

At 11 hours of age, the infant is noted to have cyanosis with breastfeeding and is found to have an oxygen saturation of 83% measured in the right upper extremity with pulse oximetry. His breathing is unlabored and lung sounds are clear to auscultation. Heart rate and rhythm are normal and no murmurs are appreciated. Blood pressures in all 4 limbs, peripheral pulses, and perfusion are also all appropriate.

The infant receives oxygen supplementation via nasal cannula, which is subsequently escalated to nasal continuous positive airway pressure (CPAP) of 6 cm H₂O with a fraction of inspired oxygen (Fio₂) of 1.00. Despite these interventions, his pulse oximetry saturations remain between 70% and 80%. Chest radiography reveals a normal cardiac size and silhouette, with clear bilateral lung fields. A complete blood cell count with differential and blood glucose concentrations is also unremarkable. Blood culture specimens are obtained and the infant starts broad-spectrum antibiotics for empirical treatment of possible early-onset neonatal sepsis.

Given the concern for congenital cyanotic heart disease, the infant is transported via air ambulance to our tertiary care children's hospital. Echocardiography performed on admission at 16 hours of age reveals normal ventricular size and function, as well as an expected patent ductus arteriosus and foramen ovale with small left-to-right shunt. An arterial blood gas measurement is obtained while the patient is receiving an Fio₂ of 1.00, which reveals a partial pressure of arterial oxygen (Pao₂) of 279 mm Hg, while the measured oxygen saturation via pulse oximeter on the right upper extremity reads only 78%. The remainder of the blood gas value is within normal limits. Repeat arterial blood gas measured while the patient is breathing room air shows a Pao₂ of 73 mm Hg.

In the midst of the medical workup, the patient's mother and maternal grandfather arrive. A detailed family history is obtained and the team learns that the infant's mother herself was hospitalized in the NICU shortly after birth for cyanosis that persisted until 5 weeks of age. The patient's grandfather states that the mother was later diagnosed with a novel fetal hemoglobinopathy that resolved over time. Her diagnosis is subsequently confirmed and a presumptive diagnosis for the patient is made.

DISCUSSION

Diagnosis

The differential diagnosis for cyanosis in a newborn is broad, but it can be delineated into 2 major categories: conditions that result in deoxygenated hemoglobin and those that are due to an abnormality in the hemoglobin molecule itself. (1) Often a first diagnostic step, the hyperoxia test is a simple clinical test that can be helpful in differentiating cardiac etiologies of hypoxemia from other causes, such as pulmonary or hematologic. For the patient in the current case, because of the presence of a high P_{aO_2} with a low pulse oximetry reading in the setting of an F_{iO_2} of 1.00, along with a normal echocardiogram and cardiac examination, it is unlikely that his cyanosis is of a cardiac or pulmonary origin. With the added family history, there is a high index of suspicion for the presence of a hemoglobinopathy, specifically a methemoglobinemia. On further review of the mother's records, it is determined that she was diagnosed with Hb FM-Fort Ripley, a fetal hemoglobinopathy. Based on this information, a presumptive diagnosis is made, "which is later confirmed by the newborn screen (Fig)." The nasal CPAP is discontinued and the infant is discharged from the hospital and continues to receive close follow-up. Over the course of the next 2 months, his cyanosis completely resolves.

The Condition

Methemoglobinemia is a rare cause of cyanosis in neonates. Methemoglobin is the altered state of hemoglobin that occurs when the ferrous iron (Fe^{2+}) is oxidized to its ferric state (Fe^{3+}) within the heme moiety of hemoglobin. (1)

Heme in the ferric state is unable to carry oxygen and leads to the clinical finding of cyanosis. (2)

Methemoglobinemia can be acquired or congenital. Acquired methemoglobinemia can be caused by a number of medications and commercially available chemicals. Acquired methemoglobinemia ranges in severity, but can be life threatening and require acute management. (3)

Congenital methemoglobinemia is very rare and can be caused by deficiencies in an essential methemoglobin reduction enzyme (NADH-cytochrome b₅ reductase) or its cofactors, or by abnormal hemoglobin variants. (3) In such cases of abnormal hemoglobin variants, known as M hemoglobins, abnormalities can be found in the α -globin, β -globin, or γ -globin chains. Most patients with hemoglobin M disease are asymptomatic and, in contrast to acquired methemoglobinemia, typically do not have any clinical sequelae and do not require any therapeutic interventions.

Depending on the globin chain affected, cyanosis from hemoglobin M disease may be present at different stages of life. In disorders in which the α -globin chain is affected, cyanosis may appear at any time, because this globin chain is present in both adult and fetal hemoglobins. In disorders affecting the γ -globin chain, cyanosis will appear during the neonatal period and will be transient, resolving when the γ -globin is replaced by β -globin and adult hemoglobin is formed. As such, when the β -globin chain is affected, cyanosis will not appear until a few months after birth when adult hemoglobin has replaced fetal hemoglobin.

Hb FM-Fort Ripley is caused by a single amino acid substitution causing a mutant γ -globin chain, leading to a

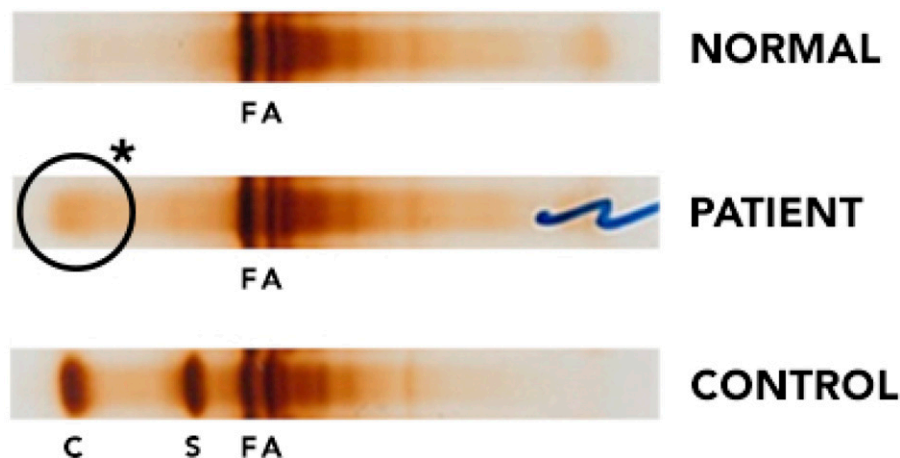


Figure. Isoelectric focusing (IEF) from newborn screen performed by the Washington State Newborn Screening Lab. The hemoglobin variant (*) was picked up on the initial IEF test. The variant band is washed out in the Hb C region and did not fully resolve. The hemoglobin variant was highly unstable and was absent on repeat confirmatory testing and so the newborn screen was reported as normal. C=Hb C; S=sickle Hb; F=fetal Hb; A=adult hemoglobin.

functionally abnormal fetal hemoglobin molecule and congenital methemoglobinemia. (4) Because the heme iron remains in the ferric state, it cannot carry oxygen and is relatively resistant to reduction by NADH-cytochrome b₅ reductase. (5) This causes slightly elevated methemoglobin levels in affected patients, leading to the primary finding of cyanosis. As it affects the γ -globin chain, it leads to cyanosis exclusively within the first few months of age and gradually improves over time as fetal hemoglobin is replaced by adult hemoglobin. (2)

Hb FM-Fort Ripley has an autosomal dominant inheritance pattern with incomplete penetrance. (6) Such a variant in the γ -globin chain may go undetected on newborn screening because of its unstable nature. The diagnosis of Hb FM-Fort Ripley has been made in some familial cases by next-generation sequencing, where a missense mutation in a single codon was found to be the source of the variant. (7)

Management

Cyanosis in patients with Hb FM-Fort Ripley typically resolves over the first few months of age with the transition to adult hemoglobin. Patients affected by this condition, as well as those with other M hemoglobins who have only mild elevations in methemoglobin levels, are typically asymptomatic. For most patients, there is no clinical sequela and no treatment is required.

Given the rarity of the condition and the challenges of quickly identifying this particular congenital methemoglobinemia, a detailed family history was key to making the diagnosis in a timely manner. Early diagnosis may allow clinicians to pursue fewer interventions after the exclusion of more serious and harmful etiologic factors. Our patient was discharged from the hospital with instructions to follow up with hematology for expectant management of the disease.

Lessons for the Clinician

- The differential diagnosis for cyanosis in a neonate is broad and should consider both disorders that lead to deoxygenated hemoglobin and those that are due to an abnormality involving the hemoglobin molecule itself.
- Methemoglobinemia can be congenital or acquired and differ in management.
- Hemoglobin M disorders can cause cyanosis at different ages, depending on the globin chain affected.
- Obtaining a family history, including the birth history of close relatives, can be critical to the diagnosis of rare conditions in neonates.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the biochemical characteristics of fetal hemoglobin.
- Know the clinical and laboratory features of neonatal hemoglobinopathies, including the thalassemias.
- Know the indications for and approaches to screening for hemoglobinopathies in the newborn population.

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3 Two-Day-Old Infant with Purulent Eye Discharge

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AUTHOR DISCLOSURE Drs Zinn, Fairchild, Kamath-Rayne, and Brady have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term male infant born via spontaneous vaginal delivery has Apgar scores of 9 and 9. Two days after birth, he is noted to have copious purulent discharge with mild conjunctival edema of the left eye and mild discharge from the right eye. Erythromycin eye ointment is administered to the neonate shortly after birth per routine protocol. Maternal medical history is noncontributory, with her obstetric record showing no history of sexually transmitted infections (STIs). Warm compresses and tear duct massage are ordered based on a suspicion of nasolacrimal duct obstruction. Overnight the infant develops increased eye drainage. On physical examination, the upper eyelids appear edematous and erythematous (left greater than right) with purulent discharge bilaterally, similar to the infant in the Fig. The conjunctivae are noted to be beefy red. Eye cultures are performed and gentamicin ointment administered.

Three days after birth, in the setting of worsening bilateral edema and copious drainage, the parents are questioned in greater detail regarding their STI history. At this time, the mother discloses that 3 days before delivery she had undergone STI testing because the infant's father had been recently treated empirically for an STI. The mother is currently unaware of her test results. Further investigation reveals that the father had presented to an outside emergency department 10 days earlier for penile discharge and dysuria, and had been treated empirically with ceftriaxone and azithromycin for urethritis. The results of the father's gonorrhea and chlamydia test are negative. The mother's STI test results are found to be positive for *Neisseria gonorrhoeae*. The preliminary results of the infant's eye



Figure. Newborn with gonococcal ophthalmia neonatorum caused by a maternally transmitted gonococcal infection. (Courtesy of Centers for Disease Control and Prevention Public Health Image Library (PHIL), identification number #3766. CDC/ J. Pledger.)

cultures reveal gram-negative diplococci. The infant is admitted to the NICU in contact isolation. A full evaluation for sepsis is initiated, including a polymerase chain reaction eye swab for chlamydia. Cefotaxime every 6 hours is started. Ophthalmology is consulted, and bacitracin ointment every 2 hours is recommended as well as balanced salt solution irrigation every 4 hours while the eye discharge is present.

DISCUSSION

Diagnosis and Hospital Course

Four days after birth, eye cultures grew *Neisseria meningitidis*. Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) test result also was positive for *N meningitidis*. Attempts at lumbar puncture were unsuccessful, while the infant's blood culture remained negative. Clinically, the infant did not demonstrate any signs of meningitis. However, due to the inability to obtain a cerebrospinal fluid specimen, infectious disease was consulted. Based on their recommendation, a 7-day course of cefotaxime treatment was started because of the inability to rule out meningitis in the setting of *N meningitidis* conjunctivitis. Staff members who came into contact with the infant were given 1 dose of ciprofloxacin prophylaxis. Several pregnant physicians who had close contact with the infant were given 1 dose of intramuscular ceftriaxone for prophylaxis. It was also recommended that the immediate family members receive prophylaxis.

The infant continued to improve and was discharged after receiving antibiotic treatment for 7 days, with recommendations for ophthalmology follow-up 1 week after discharge. After the initial treatment plans were under way, the remaining records and laboratory results of the infant's father were obtained. The father's urine culture from his previous evaluation for penile discharge was positive for *N meningitidis*.

The Condition

Neonatal conjunctivitis (NC), or ophthalmia neonatorum, is an inflammatory disease characterized by erythema, swelling, and discharge of the conjunctiva that can occur in the first 4 weeks after birth. It affects between 1.6% and 12% of all newborns. (1) NC may be a result of any of the following: bacterial infection, viral infection, or a reaction to allergens or chemicals.

Common causes of acute bacterial NC include *Chlamydia trachomatis* and *N gonorrhea* transmitted at birth. *N meningitidis* is an uncommon causative organism of acute conjunctivitis. Primary meningococcal conjunctivitis (PMC) is thought to occur because of the direct inoculation of *N*

meningitidis into the conjunctival sac from an exogenous source. (2)(3)(4) PMC can precede invasive disease, serving as a mechanism for neonatal meningitis. (4)(5) Although more widespread vaccination has led to an overall decrease in invasive meningococcal disease, several studies and health clinics have reported increasing incidence of *N meningitidis* isolated from the genitourinary tract. (5)(6)(7) Due to the risks of invasive meningococcal disease, both with meningococcal and gonococcal conjunctivitis in infants, cultures should be performed of the purulent ocular discharge, blood, and cerebrospinal fluid when there is suspicion for *Neisseria* conjunctivitis. Unlike gonococcal conjunctivitis, there is no consensus on the treatment recommendations for PMC.

Previous literature shows that patients treated with topical therapy alone were 19 times more likely to develop systemic disease. (4) Therefore, systemic antibiotic therapy is necessary, and topical therapy may be used as an adjunct. Recommendations for systemic meningococcal disease are to begin empirical treatment with an extended-spectrum cephalosporin, such as cefotaxime, and switch to narrow-spectrum penicillin G once meningococcal disease is established, for a total of 5 to 7 days. (8) No consensus has been established for treatment duration.

Lessons for the Clinician

- It is important to consider *Neisseria meningitidis* when evaluating neonatal conjunctivitis, because distinguishing between *Neisseria gonorrhoeae* and *N meningitidis* has significant implications on treatment course as well as the need for prophylaxis of close contacts.
- With increased screening for sexually transmitted infections and possible increasing incidence of *N meningitidis* isolated from the genitourinary tract, there likely could be an increase in cases and/or misdiagnoses of meningococcal conjunctivitis.
- Patients with meningococcal infections should be placed in droplet isolation while instituting standard precautions until 24 hours after initiation of effective antimicrobial therapy. Chemoprophylaxis is recommended for close contacts including individuals with direct exposure to patient secretions, unprotected contact during endotracheal intubation, household contacts, or those frequently sleeping in the same dwelling as index patient.
- Chemoprophylaxis includes rifampin for 2 days for children or adults or a single dose of ciprofloxacin for adults. A single dose of azithromycin can be used with ciprofloxacin resistance. Intramuscular ceftriaxone is recommended for pregnant women.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of neonatal *Neisseria gonorrhea* infections.
- Know the clinical manifestations, diagnosis, management, and complications of neonatal *N gonorrhea* infections.
- Know the benefits and complications of eye prophylaxis (eg, obstructed nasolacrimal duct).
- Know the causes and clinical and laboratory features of acute neonatal infections of the eyes, including ophthalmia neonatorum.

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Parent Resources from the AAP at HealthyChildren.org

- Heart Disease: Reduce Your Child's Risk: <https://www.healthychildren.org/English/health-issues/conditions/heart/Pages/Heart-Disease.aspx>
- Screening & Treating Kids for High Blood Pressure: AAP Report Explained: <https://www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx>
- Detecting Urinary Tract Infections: <https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Detecting-Urinary-Tract-Infections.aspx>
- Prevent Urinary Tract Infections in Children: <https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Prevent-Urinary-Tract-Infections-in-Children.aspx>
- Sleep Apnea Detection: <https://www.healthychildren.org/English/ages-stages/baby/sleep/Pages/Sleep-Apnea-Detection.aspx>
- The Truth About Home Apnea Monitors for SIDs: <https://www.healthychildren.org/English/ages-stages/baby/sleep/Pages/Home-Apnea-Monitors-for-SIDs.aspx>

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Index of Suspicion in the Nursery

3 Two-week-old Male Infant with Progressive Emesis

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AUTHOR DISCLOSURE Drs Stoner and Cutlan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Stoner, currently a pediatric critical care Fellow at Children's Mercy Kansas City, was a pediatric resident with Marshfield Clinic in Marshfield, WI, when she wrote this article.

PRESENTATION

A 14-day-old term white male infant presents to his primary pediatrician's office with a 3-day history of progressive emesis, which is described by his mother as nonbloody and nonbilious in nature. The mother reports that emesis is frequently associated with feeding and occasionally projectile in nature, with 8 to 10 episodes in the last 24 hours. It is reported that he is taking 2 ounces of expressed human milk every 2.5 hours. His urine and stool output is adequate. The pregnancy was uncomplicated, but labor was complicated by mild shoulder dystocia. The infant's birthweight was 3,980 g. His blood type is B negative and direct antiglobulin testing positive, with Apgar scores of 5 and 10 at 1 and 5 minutes, respectively, requiring only tactile stimulation for resuscitation. He was discharged from the hospital 2 days after birth with a portable phototherapy device for jaundice, which was required for 3 days.

On examination, his weight is 3,920 g, not back to birthweight. He is afebrile, with otherwise unremarkable vital signs and has mild jaundice without icterus. He demonstrates signs of mild dehydration with sunken anterior fontanelle and mildly delayed capillary refill; the remainder of the examination findings were unremarkable. Based on the patient's history of voluminous and projectile emesis with inadequate weight gain, pyloric stenosis is the primary concern. Abdominal ultrasonography reveals the diagnosis.

Ultrasonography demonstrates a normal pylorus with bilateral adrenal masses, greater on the right than the left, with no obvious internal blood flow. The infant is hospitalized for a partial evaluation for sepsis, including complete blood cell count, which demonstrated a hemoglobin of 13.4 g/dL (134 g/L), hematocrit of 38.2% (0.38), platelets of $529 \times 10^3/\mu\text{L}$ ($529 \times 10^9/\text{L}$), and white blood cell count of $15,400/\mu\text{L}$ ($15.4 \times 10^9/\text{L}$) with normal differential. C-reactive protein, urine analysis with urine culture, and serum electrolytes are found to be normal. In addition, blood culture and chest radiography are unremarkable.

DISCUSSION

Differential Diagnosis

Pyloric stenosis must be high on the differential diagnosis given this infant's presentation; however, on discovery of the bilateral adrenal masses, an extensive differential diagnosis must be considered, which includes neuroblastoma, Wilms tumor, teratoma, adrenal abscess, vascular thrombosis, congenital adrenal cystic lesion, subdiaphragmatic extralobar pulmonary sequestration, and adrenal hemorrhage (infectious or traumatic). (1)(2) Laboratory studies and imaging can aid in

narrowing the differential. In our patient, imaging revealed no demonstrable blood flow to either mass, making the most likely diagnosis resolving adrenal hemorrhage. (1) This was confirmed on serial imaging that displayed resolving adrenal hematomas.

The Condition

Neonatal adrenal hemorrhage (NAH) is defined as hemorrhage into the adrenal gland prenatally or within the first few weeks after birth. (3) Historically it has been described as a rare clinical entity with an incidence of 1.7 to 2.1 per 1,000 autopsies of newborn infants. However, more recently, the incidence has been described as up to 3% among infants who have been subjected to screening ultrasonography. (4) (5) This discrepancy is thought to be because many of the affected infants are asymptomatic, and the hemorrhage resolves without clinical signs or symptoms. The hemorrhage typically is unilateral, involving only the right side. (1)

There are important anatomic considerations to understanding the underlying pathophysiology of NAH. The neonatal adrenal gland is relatively large in size relative to body weight. The adrenal gland is an extremely vascular organ, with 50 to 60 arterial branches. Each gland contains a subcapsular plexus that drains into a medullary sinus via few venous channels, thereby increasing the chances of vascular damming during surges of increased blood flow. In stressful situations, adrenocorticotrophic hormone (ACTH) secretion increases, which stimulates adrenal arterial blood flow and adrenal vein spasm. (3) The limited venous drainage capacity may cause venous stasis, leading to hemorrhage. The predominance of right-sided involvement has been hypothesized to be related to 2 factors: the right adrenal vein drains directly into the inferior vena cava and is, therefore, sensitive to changes in venous pressure. (1)(5) In addition, the anatomic location of the right adrenal gland between the liver and spine places it at risk for compression during delivery.

Adrenal hemorrhage can be a significant condition found incidentally. (1) Typical presentation includes persistent neonatal jaundice, anemia, abdominal mass, flank mass, painful swelling of scrotum with or without bluish discoloration, scrotal hematoma, vomiting, poor feeding, and rarely, shock or adrenal crisis. (4)(6). NAH rarely leads to adrenal insufficiency in term newborns unless more than 90% of the total adrenal volume is affected. (7) If adrenal insufficiency does occur, it typically resolves secondary to the regenerative capacity of the adrenal gland. (6)

Close follow-up by endocrinology is essential. In our patient, an endocrinology evaluation for adrenal insufficiency was undertaken. Random cortisol was found to be 18.3 $\mu\text{g/dL}$ (504.8 nmol/L; reference range 3–11 $\mu\text{g/dL}$

[82.7–303.4 nmol/L]) and early morning ACTH was 108 pg/mL (23.7 pmol/L; reference range 0–46 pg/mL [0–10.1 pmol/L]). ACTH stimulation test revealed an adequate response. Aldosterone was found to be elevated at 198.6 ng/dL (5,509 pmol/L; reference range 3–34 ng/dL [83–943 pmol/L]) with normal-for-age renin at 30.17 ng/mL (0.7 pmol/L), indicating no evidence of mineralocorticoid deficiency. Due to persistent ACTH elevation, the patient was discharged from the hospital with instructions to provide stress dose steroids for episodes of emesis, temperatures greater than 100.4°F (38°C), or any illness accompanied by poor feeding and lethargy. He continued to receive outpatient follow-up by endocrinology. Serial abdominal ultrasonography demonstrated complete resolution of the left adrenal hematoma and almost complete resolution of the right adrenal hematoma at 2 months' time.

Prognosis

Treatment of NAH is typically supportive; however, in the instance of adrenal insufficiency, it may be necessary to provide stress dose maintenance steroid therapy until full recovery of the adrenal gland is achieved. (7) The typical course of a healthy neonate ranges from asymptomatic to mild clinical presentation with spontaneous regression of the hematoma without significant sequelae. (1)

Lessons for the Clinicians

- Neonatal adrenal hemorrhage (NAH) is likely more common than previously described, and goes undiagnosed because of the nonspecific presenting signs and symptoms.
- NAH rarely results in adrenal insufficiency, because it rarely affects more than 90% of total adrenal gland volume. If adrenal insufficiency does occur, it typically resolves spontaneously because of the regenerative nature of the neonatal adrenal gland.
- Treatment is typically supportive; however, steroid therapy may be required for a limited period, until the adrenal gland is able to recover.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the differential diagnosis of bilious and nonbilious vomiting and abdominal distention in the neonate.

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Parent Resources from the AAP at HealthyChildren.org

- Infant Vomiting: <https://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Infant-Vomiting.aspx>

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

Case 3: Two-week-old Male Infant with Progressive Emesis

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2 Umbilical Cord with Five Openings

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AUTHOR DISCLOSURE Drs Singh, Kler, and Thakur have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is delivered at 34 weeks of gestation to a gravida 2 woman by cesarean section in view of vaginal leaking and oligohydramnios. There are no other antenatal complications. The infant cries immediately after birth and does not require resuscitation. She has a birthweight of 1,850 g (16th percentile), length of 45 cm (54th percentile), and occipitofrontal circumference of 31 cm (47th percentile). In view of the respiratory distress and excessive frothing from the mouth, insertion of an orogastric tube is attempted, which does not go beyond 10 cm. The infant is transferred to the Neonatal Intensive Care Unit (NICU) for further management. On physical examination, she is alert and has no dysmorphic features or physical deformity, but persisting respiratory distress and frothing from the mouth require repeated suctioning. Chest radiography is performed with the orogastric tube in situ, which reveals coiling of tube in the esophagus with the presence of gas shadows in the abdomen, suggestive of esophageal atresia with tracheoesophageal fistula. A thorough physical examination, abdominal ultrasonography, and echocardiography are performed to rule out the VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities). The infant undergoes repair of esophageal atresia and tracheoesophageal fistula at 36 hours after birth and a transanastomotic tube is placed during surgery. After surgery, she receives mechanical ventilation and is hemodynamically stable. Considering the need for ventilation and parenteral nutrition, central line (umbilical catheters) insertion is planned. The cord clamp is present around 4 cm above the umbilicus. The cord stump looks normal. The cord is cut just below the clamp, and to our surprise, we find 5 openings, with 1 opening being larger than normal with thicker walls, but no bleeding (Fig).

DISCUSSION

Progression

As soon as the catheter is introduced into the umbilical stump, a streak of meconium is seen on the surface of the catheter. Suspecting it to be patent vitellointestinal duct (VID), the catheter is removed. It is realized that the openings seen are 2 umbilical arteries and 2 umbilical veins, along with 1 opening of the patent VID. The base of the umbilical stump is clamped, and a peripherally inserted central catheter is placed.

Feeding is started on the second postoperative day through the transanastomotic tube and is well tolerated. The infant undergoes extubation 72 hours after surgical repair. She remains stable on room air. Postoperative contrast study is performed on day 7, which shows no leakage of dye. The transanastomotic tube is



Figure. Umbilical cord showing 5 openings.

removed and the infant is started on breast milk feedings. She is discharged from the hospital on day 12 after birth.

Diagnosis

The infant is seen for follow-up on day 15. The umbilical cord has fallen off and there is no discharge from the umbilical stump. This is a case of patent VID.

The Condition

VID is an embryonic structure that connects the developing midgut to the primitive yolk sac. Normally, it becomes a fibrous band and disintegrates at 5 to 10 weeks of gestation. If it fails to completely atrophy, then various anomalies termed VID remnants can result. VID remnants include patent VID (umbilical fistula), Meckel diverticulum, vitelline sinus, vitelline cyst, umbilical polyp, and fibrous remnants. (1) These anomalies may persist in 2% of infants. (2) Associated anomalies include cardiac defects, congenital diaphragmatic hernia, duodenal atresia, esophageal atresia, imperforate anus, gastroschisis, malrotation, omphalocele, Hirschsprung disease, and Down syndrome. Meckel diverticulum is the most common VID anomaly. (3)

The clinical presentation of VID remnants is variable. Patients with these anomalies may remain asymptomatic throughout life or may present with serious complications, especially during infancy and early childhood for boys. The main presentations are bleeding from the gastrointestinal tract, obstruction, and diverticulitis.

A patent VID can present as discharging umbilical sinus, umbilical nodule or polyp, bleeding from intestinal mucosa, and intestinal small bowel prolapse. The incidence of patent VID has been reported to be 0.0063% to 0.0067%. (4) Just after birth, it can present with serosanguinous, feculent, or bilious discharge from the umbilicus or as an extra opening in the umbilical cord. If the defect is wide enough, it can result in prolapse of intestine through it. (5) In suspicious cases, ultrasonography, injecting contrast material into the patent tract, and roentgenography helps in the diagnosis. Treatment of patent VID is surgical excision in uncomplicated cases. In cases that present with complications, a part of the intestine may need to be removed, depending on perioperative findings. As seen in the current case, this condition can be missed at the time of birth in the delivery room, but it can be managed later by using another clamp and following its course. The VID spontaneously resolved, and no discharge occurred from the umbilicus in follow-up examination until 6 months.

Lessons for the Clinician

1. Careful inspection of umbilical openings is required at the time of birth.
2. The cord should be palpated before catheter insertion for abnormal thickening and cut away from its base for catheter insertion.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know how to evaluate and manage disorders of the umbilical cord, including granulomas, persistent omphalomesenteric duct remnant, and patent urachus.

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Case 2: Umbilical Cord with Five Openings

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Unexplained Hypercarbia in a Neonate in the Neonatal Intensive Care Unit

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PRESENTATION

AUTHOR DISCLOSURE Drs Nanda, Bandiya, Nangia, and Berry-Kravis have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A male infant is delivered at term via lower-segment cesarean delivery with a birthweight of 3.5 kg to a 25-year-old gravida 2 woman. The mother did not have any significant events during the antenatal period but was noted to have polyhydramnios (amniotic fluid index, 33) during the third trimester. There is no history of consanguinity or sibling death. The infant cried after birth, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The infant is transferred to the postnatal ward and begins breastfeeding. He develops central cyanosis 3 hours after birth and is admitted in the NICU. His vital signs at the time of admission are as follows: temperature, 97.8°F (36.6°C); heart rate, 128 beats/min; respiratory rate, 36 breaths/min; capillary refill time, 2 seconds; peripheral pulses, palpable; and oxygen saturation, 72% in room air, which improved with oxygen supplementation. The infant is limp at the time of admission, but improves after oxygen administration. The infant has intermittent stridor. He has repeated episodes of apnea on day 2 after birth, for which he was given pressure-synchronized intermittent mandatory ventilation with minimal settings. Antibiotics are started and a blood sample is sent for culture. Venous blood gas before intubation is suggestive of respiratory acidosis with normoxemia (pH 6.86, partial pressure of carbon dioxide [Pco₂] 144 mm Hg [19.15 kPa], partial pressure of oxygen [Po₂] 54 mm Hg [7.18 kPa], lactate 3.5 mg/dL [0.39 mmol/L]), which improves within 1 hour of ventilation (pH 7.34, Pco₂ 36.4 mm Hg [4.8 kPa], Po₂ 88 mm Hg [11.7 kPa], lactate 3.5 mg/dL [0.39 mmol/L]).

Clinical possibilities considered include early-onset sepsis, pneumonia, perinatal asphyxia, meningitis, congenital heart disease; congenital anomalies like esophageal atresia with/without tracheoesophageal fistula; airway anomalies; vocal cord palsy; subglottic stenosis; and inborn errors of metabolism. Investigations are begun accordingly.

The infant has normal blood glucose (112 mg/dL [6.2 mmol/L]) and serum calcium (4.4 mg/dL [1.1 mmol/L]) values; his hematocrit is 47.5%; sepsis screening result is negative (total leukocyte count 27,100/μL [27.1 × 10⁹/L], absolute neutrophil count 19,000/μL [19 × 10⁹/L], microerythrocyte sedimentation rate 8 mm in the first hour, C-reactive protein negative, immature to total neutrophil ratio 0.15); cerebrospinal fluid cytologic findings are normal; and biochemistry results are normal (no cells, glucose 168 mg/dL [9.3 mmol/L], protein 0.118 g/dL [1.18 g/L]). Head ultrasonography, chest radiography, and echocardiography do not reveal any abnormality. Blood culture is sterile. The epiglottis and vocal cord movement are normal.

under direct laryngoscopy. Findings of trimethylsilyl and gas chromatography/mass spectrometry are within normal limits.

PROGRESSION

The infant is hemodynamically stable with ventilatory support and undergoes extubation and is given nasal continuous positive airway pressure (CPAP) 3 days after birth. He develops apnea within 30 minutes of extubation, undergoes reintubation, and mechanical ventilation is restarted using the previous settings. Venous blood gas before intubation shows respiratory acidosis (pH 6.94, P_{CO_2} 119 mm Hg [15.86 kPa], bicarbonate 24.8 mEq/L [24.8 mmol/L], lactate 3.9 mg/dL [0.43 mmol/L]), which improves after 1 hour of ventilation (pH 7.35, P_{CO_2} 40.5 mm Hg [5.39 kPa], bicarbonate 22 mEq/L [22 mmol/L], lactate 3.9 mg/dL [0.43 mmol/L]). The infant continues to receive ventilatory support, and bronchoscopy and chest computed tomography (CT) are planned to rule out any congenital airway anomalies. Bronchoscopy shows normal anatomy of airway. Antibiotics are continued, along with mechanical ventilation. Another trial of extubation to nasal CPAP fails on day 9 after birth. The infant develops respiratory acidosis with apnea (pH 6.99, P_{CO_2} 119 mm Hg [15.86 kPa], bicarbonate 27.3 mEq/L [27.3 mmol/L], lactate 1.8 mg/dL [0.2 mmol/L]), which improves after ventilation (pH 7.56, P_{CO_2} 25 mm Hg [3.3 kPa], bicarbonate 22.1 mEq/L [22.1 mmol/L], lactate 3.6 mg/dL [0.4 mmol/L]). Contrast-enhanced chest CT reveals multiple patchy subsegmental atelectasis in the right upper, right middle, and left lower lobes. Brain magnetic resonance imaging findings are normal. Culture from bronchoalveolar fluid is sterile. The infant undergoes extubation on day 15 after birth and receives noninvasive positive pressure ventilation (NIPPV) support with minimal settings. Trial of extubation to nasal CPAP is unsuccessful. Neurologic findings are normal. The infant is discharged against medical advice in view of financial constraints.

The neonate has multiple episodes of apnea requiring ventilatory support, has evidence of hypoventilation with hypercarbia, but no associated increase in respiratory rate in response to hypercarbia; the systemic examination including the respiratory, cardiac, and central nervous systems and metabolic profile are within normal limits. Hence, a central cause of hypoventilation is suspected and investigated.

Genetic study is performed using the peripheral blood sample. Whole cellular DNA is extracted from blood and polymerase chain reaction analysis is conducted of the region in exon 3 of *PHOX2B* gene containing the polyalanine-coding repeat tract. The infant is found to have a normal allele coding for 20 and an expanded allele coding for

26 polyalanine repeats, suggestive of congenital central hypoventilation syndrome (CCHS).

DISCUSSION

CCHS, also known as the *Ondine curse*, is a rare disease with failure of autonomic nervous system. The first infantile case was reported in 1970 by Mellins et al. (1) The basic pathology is related to generalized autonomic nervous system failure. Associations with Hirschsprung disease, esophageal dysmotility, decreased heart rate variability, and ocular and pupillary abnormalities have been reported. (2)(3)

The basic genetic mutation involves the *PHOX2B* gene located in chromosome 4p12. (4)(5)(6) Nearly 90% of the cases are heterozygous for a polyalanine repeat expansion mutation (PARM). (5)(6) Among PARMs, the 20/25, 20/26, and 20/27 genotypes are the most common. (3) The remaining 10% of cases are heterozygous for a non-PARM, which includes frameshift, missense, or nonsense mutations. Most non-PARM mutations are associated with a severe phenotype, including Hirschsprung disease, need for continuous ventilatory support, and risk for tumors of neural crest origin.

Patients with CCHS present with hypoventilation and hypoxemia. These abnormalities are more marked during sleep. The degree of hypoventilation is dependent on the state and is more marked during non-rapid eye movement sleep. (3) These infants have blunted response to hypercarbia and hypoxia. The clinical features that characterize CCHS include intermittent cyanosis with measurable hypercapnia. The cases do not show the normal increase in respiratory rate in response to hypercarbia nor do they appear to be in distress.

The clinical features also depend on the specific genotypes. (7) Children with the 20/27 to 20/33 genotypes and the non-PARMs usually require continuous ventilatory support. Children with the 20/26 genotypes have a variable ventilator dependency during the awake state, which depends on the level of activity. Those with the 20/24 or 20/25 genotype rarely require continuous respiratory support. The symptoms of autonomic nervous system disorders increase with an increase in the length of polyalanine repeat. Hirschsprung disease is reported in 87% to 100% of cases with non-PARMs in contrast to 13% to 20% of PARMs. Tumors of neural crest origin are more common with non-PARMs (50%) than PARMs (1%). Among PARMs, only children with the 20/29 or 20/33 genotypes have been identified to have tumors of neural crest origin, such as ganglioneuroma and ganglioneuroblastoma.

The primary goal of management involves securing the airway and ensuring adequate ventilation. The disease neither resolves spontaneously nor responds to any pharmacologic stimulants. Because these patients do not have any lung

pathology, a wide variety of respiratory support modalities, such as positive pressure ventilation through tracheostomy, bilevel positive airway pressure through nasal or face mask, negative pressure ventilation, and diaphragmatic pacing, can be used in these patients. To optimize quality of life, these children need available energy for other academic and physical activities. Although the patients can occasionally be treated with noninvasive respiratory support, the American Thoracic Society recommends positive pressure ventilation via tracheostomy in the first several years after birth. (5)(8) Tracheostomy tube smaller than the airway caliber may be preferred to reduce the chances of tracheomalacia, and also allowing a margin of safety in case of blockade of the tube. Noninvasive respiratory modalities are smaller in size, easier to use, and less expensive but usually are not considered for respiratory support during the initial years after birth. However, such modalities may be considered in stable patients who require respiratory support only during sleep. Even in these cases these modalities are not considered for conservative management until age 6 to 8 years at the earliest.

The current case presented with recurrent episodes of unexplained apnea associated with hypercarbia. The infant did not have any evidence of Hirschsprung disease or features suggestive of other autonomic nervous system disorders. His condition was managed with invasive ventilatory support initially and later with NIPPV because of the parents' desire to avoid tracheostomy. This case was a PARM with the 20/26 genotype, one of the most common genotypes of CCHS.

Lessons for the Clinician

- The diagnosis of congenital central hypoventilation syndrome (CCHS) should be suspected in cases of hypoventilation during infancy, particularly when no obvious abnormalities are detected in the other systems including respiratory, cardiovascular, and central nervous systems.
- The diagnosis of CCHS should be confirmed with the study of *PHOX2B* gene mutation.
- The parents of patients with CCHS should be tested for the *PHOX2B* mutation to determine the risk for subsequent children.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects of pulmonary reflexes and oxygen, carbon dioxide, and hydrogen ion concentrations on control of neonatal breathing.

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Case 2: Unexplained Hypercarbia in a Neonate in the Neonatal Intensive Care Unit

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Index of Suspicion in the Nursery

1 Upper Gastrointestinal Hemorrhage in a Healthy Term Infant

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AUTHOR DISCLOSURE Drs Ahamed, Yu, Batton, and Nimavat have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A female infant is born via spontaneous vaginal delivery at 40 weeks of gestation to a 34-year-old multigravida who has diet-controlled gestational diabetes. Meconium-stained amniotic fluid is noted with rupture of membranes 3 hours before delivery. The infant is vigorous after birth, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The neonate's birthweight is 4,050 g (98th percentile). The initial physical examination findings are normal and she is allowed to room in with her mother. Vitamin K is administered within 1 hour of birth.

Due to ineffective attempts at lactation, the neonate receives supplementation with term formula once during the first 24 hours. There is no documented void before 24 hours and a neonatology consultation is requested. During the physical examination in the newborn nursery, at 26 hours of age, she passes a large bloody stool with a significant amount of bright red blood. The infant appears well and nondistressed, with normal vital signs, good perfusion, and no respiratory distress. The abdomen is soft, nondistended, and nontender. No anal fissures are noted. Her examination findings are otherwise unremarkable. Review finds that she also had an episode of brownish emesis earlier in the day, which is attributed to swallowed maternal blood. The infant is transferred to the NICU.

An Apt-Downey test on the stool could not be performed because the sample was contaminated with meconium and red blood cells could not be eluted. Laboratory results are as follows: hemoglobin, 14.1 g/dL (141 g/L); hematocrit, 40.8%; platelet count, $244 \times 10^3/\mu\text{L}$ ($244 \times 10^9/\text{L}$); C-reactive protein, 3.4 mg/dL (32.3 nmol/L); prothrombin time, 16.6 seconds; and partial thromboplastin time, 31.6 seconds. An abdominal radiograph demonstrates a normal bowel gas pattern. A Replogle tube is placed and it drains blood-stained fluid. She is given nothing by mouth, started on intravenous fluids, and administered empirical antibiotics after obtaining a blood culture.

Over the next 8 hours, the infant continues to pass several large bloody stools with blood clots. Approximately 110 mL of blood-stained gastric fluid is drained from the stomach. The hemoglobin level decreases to 9.3 g/dL (93 g/L) during this time. However, she is not tachycardic and her blood pressure remains normal with normal peripheral perfusion. Between 24 and 48 hours of age, 40 mL/kg of crystalloid boluses and 40 mL/kg of packed red blood cells are administered because of the continuing drop in the hemoglobin level; pediatric surgery, gastroenterology, and hematology are consulted.

DISCUSSION

Diagnosis

Localizing the source and causes of gastrointestinal (GI) bleeding in a well-appearing term infant can be challenging. The most likely cause is swallowed maternal blood, which can be confirmed by performing an Apt-Downey test. Although results of this test were not available in this case, the decreasing hemoglobin level, bloody stool noted on gross examination, and bloody Replogle drainage strongly suggested a pathologic cause of upper GI tract bleeding. The differential diagnoses included bleeding due to hepatic failure, hematologic conditions, infection, necrotizing enterocolitis, hemorrhagic gastritis, esophagitis, gastric ulcer, Meckel diverticulum, an arteriovenous malformation (AVM), or other rare anomalies of the GI tract. Bleeding from a hepatobiliary source or due to a hematologic condition seemed unlikely because of the normal coagulation profile and platelet count and the absence of hepatosplenomegaly. Infections such as sepsis and necrotizing enterocolitis also seemed unlikely because the infant appeared to be well, there were few risk factors for infection, and radiographs of the chest and abdomen were unremarkable. Although uncommon in newborns, hemorrhagic gastritis was considered the most likely etiology in our infant based on the large amount of bleeding and her overall condition. An AVM, gastric ulcer, and Meckel diverticulum remained considerations.

Course

In consultation with the pediatric gastroenterologist, intravenous pantoprazole was started as presumptive treatment of hemorrhagic gastritis. Because the infant was hemodynamically stable and did not have any evidence of coagulopathy, invasive procedures such as exploratory laparotomy or upper GI endoscopy and further imaging studies to evaluate and treat other causes such as an AVM or Meckel diverticulum were deferred.

Once pantoprazole was initiated, within 12 hours, the volume of bloody gastric aspirate reduced and turned clear between 48 and 72 hours. Blood was no longer grossly visible in the stool and by postnatal day 5 the stools were no longer guaiac positive for blood. The Replogle tube was removed on postnatal day 4, and feeds were introduced and advanced uneventfully beginning on day 5. Intravenous pantoprazole was given for 5 days followed by oral dosing. She was discharged from the hospital on postnatal day 7 on oral pantoprazole. At 2 months of age, she had not had any recurrence of GI bleeding and had achieved good growth and development.

The Condition

Upper GI bleeding is defined as GI bleeding proximal to the ligament of Treitz. Approximately 20% of GI bleeding in children is from an upper GI source. Significant upper GI bleeding is uncommon in healthy term neonates. When it does occur, the most common presentation is hematemesis or bloody gastric aspirates, but bright red blood in the stools has also been reported due to the rapid intestinal transit in neonates.

In healthy-appearing term neonates, hematemesis or bloody gastric aspirates are almost always caused by swallowed maternal blood. This diagnosis can be made by performing an Apt-Downey test which detects the presence of fetal cells in either the gastric aspirate or stools. The most common pathologic causes of neonatal upper GI bleeding are esophagitis and gastritis. Most cases of esophagitis and gastritis are, however, asymptomatic, with only 6% to 12% of the children in intensive care presenting with significant lesions to cause any GI bleeding. These cases tend to present with blood-tinged emesis and usually resolve spontaneously. Significant upper GI bleeding associated with hypovolemia, shock, and death is usually related to perinatal stress, hypoxemia, respiratory failure, congenital heart disease, raised intracranial pressure, or infection. Additional rare causes that have been reported include coagulopathy due to liver dysfunction, portal venous thrombosis leading to an esophageal variceal bleed, hemorrhagic disease of the newborn due to vitamin K deficiency, intestinal duplication, or an AVM. Milk protein intolerance is usually associated with lower GI bleeding typically beyond 7 days of age, though it can sometimes present with esophagitis.

Gastric ulcers are rare among infants in the neonatal period. When they do occur, they are usually secondary to an underlying illness; however, the origin of stress-induced gastric lesions in infants is poorly understood. Few cases of massive upper GI bleeding due to hemorrhagic gastritis in otherwise healthy infants have been reported.

The mainstay in management for an infant with GI bleeding is restoring and maintaining hemodynamic stability. Crystalloid fluid boluses and blood transfusions should be administered judiciously and rapidly to ensure adequate perfusion. With the advent of smaller endoscopes, esophagogastroduodenoscopy may be considered to diagnose and treat the source of GI bleeding. This procedure is relatively safe, but potential therapeutic benefits may be limited by the small size of the scope required for a neonatal procedure. Use of an H₂ blocker such as ranitidine has been shown to be beneficial in controlling mild to moderate upper GI bleeding within 24 to 48 hours with no recurrence

of episodes of bleeding. In a case control study of infants who presented with upper GI bleeding, the mucosal lesions were noted to resolve in 75% of patients within 28 days of the use of H₂ blockers. Data regarding the use of proton pump inhibitors in neonates are limited. Both of these classes of medications reduce gastric acid secretion and increase the pH of gastric contents. In rare instances, bleeding cannot be controlled with conservative management, and endoscopy or exploratory laparotomy may be required.

Lessons for the Clinician

- Upper GI bleeding in a healthy term infant can be a diagnostic challenge.
- When upper GI bleeding is not the result of swallowed maternal blood, extensive evaluation should be performed to identify the cause.
- If hemorrhagic gastritis is suspected and the neonate is hemodynamically stable without significant coagulopathy, a trial of an H₂ blocker or proton pump inhibitor may be considered before proceeding with more invasive evaluation and treatment.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations and differential diagnosis of GI bleeding in newborn infants, including the various coagulation disorders that cause GI hemorrhage.

Suggested Readings

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Index of Suspicion in the Nursery

2 Vesicular Lesions of the Oral Mucosa

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AUTHOR DISCLOSURE Drs Weber, Delle Donne, and Delaney have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A term female infant (39+4 weeks) with a birthweight of 3,055 g is born via spontaneous delivery to a gravida 4, para 3 woman. Maternal history is significant for Ashkenazi Jewish heritage and known connective tissue disease requiring plaquenil. Maternal serologies and prenatal testing are unremarkable with the exception of herpes simplex virus (HSV) 1 immunoglobulin (Ig) G being positive and IgM inconclusive. The mother was not taking antiviral therapy during pregnancy or at delivery. On admission to the labor and delivery department, the infant's mother is without prodromal symptoms or genital lesions concerning for HSV. The patient is born via spontaneous vaginal delivery through meconium-stained amniotic fluids, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. At the time of delivery, the infant has normal physical examination findings and is kept in the mother-baby unit for routine newborn care.

At about 30 hours after birth, the newborn team is called to the bedside by the nurses because of the development of vesicular lesions on the oral mucosa of the lower lip (Fig). On examination of the oral mucosa, multiple vesicular lesions are noted, which measure 1 to 2 mm in size. Because of the history of HSV-1 without antiviral suppression and the character of the lesions, a full evaluation for HSV (skin-eye-mouth disease vs disseminated disease) is initiated, and the infant is transferred to the NICU. Cerebrospinal fluid (CSF) and blood specimens are obtained for HSV polymerase chain reaction (PCR) testing. Skin and mucosal swabs for viral cultures are completed. Laboratory testing is ordered for complete blood cell count, C-reactive protein, and comprehensive metabolic panel for further screening. High-dose acyclovir is started for empirical coverage while results are pending. Dermatology and pediatric infectious disease (ID) specialists are consulted for further evaluation.

DIFFERENTIAL DIAGNOSIS

HSV presents with clear vesicular lesions that can present on the skin, eyes, or mucosa. HSV can also cause a disseminated infection. (1) Maternal infections can be passed to neonates, with mortality rates of up to 29%, even with treatment. (1) Whenever HSV is suspected, the standard of care is to empirically treat with high-dose acyclovir. Neonates must be treated until maternal testing shows negative results or empirical treatment is given for 14 to 21 days pending clarification of primary versus secondary infection. (2) HSV can be diagnosed with PCR, direct fluorescent antibody (DFA), and viral cultures. Histologic studies show reticular epidermal degeneration, acanthosis, and intraepidermal vesicle formation. Other findings include intranuclear inclusion bodies and multinucleate giant keratinocytes. (3)

Other benign entities that could present with vesicular lesions, as in this patient, are lymphangiomatous malformations and sebaceous hyperplasia. Microcystic

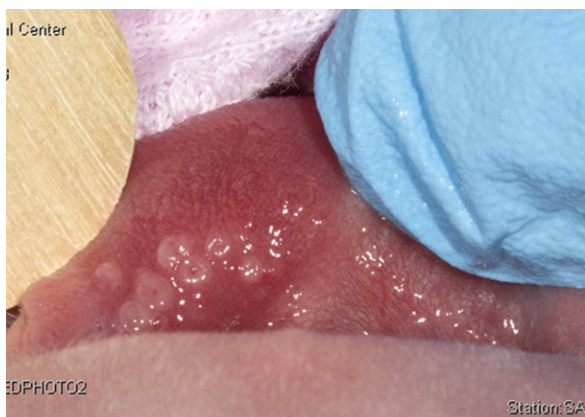


Figure. Vesicular lesions of oral mucosa.

lymphangiomatous malformations are benign tumors of the lymphatic system. Lesions are deep-seated vesicles described as “frog-spawn.” Vesicles can be clear to purple in color. These lesions grow slowly and may bleed. For large malformations, surgery may be required. Histologic studies show dilated lymphatic vessels with dilated blood vessels in the upper dermis. (3)

Sebaceous hyperplasia presents with yellow-white micro-papules with central umbilication. Sebaceous hyperplasia is a benign growth that can be present at birth and usually resolves within the first few weeks after birth. (4) Sebaceous hyperplasia is thought to be caused by maternal androgen levels. Histologic studies show proliferation of sebaceous lobules in the dermis.

DIAGNOSIS

The patient was ultimately diagnosed as having sebaceous hyperplasia. Sebaceous hyperplasia is a relatively common finding in newborn infants. Most cases of sebaceous hyperplasia resolve spontaneously as maternal androgen levels decrease in the infant. (4) Although a benign dermatologic finding resolves, one cannot rule out other causes when initial lesions appear as vesicles. When diagnosed with sebaceous hyperplasia, infants do not routinely need dermatology follow-up.

PROGRESSION

The infant received high-dose acyclovir for 4 days while undergoing an evaluation for HSV. Dermatology evaluated the infant and further described lesions as white-yellow papules without scarring. A lesion was unroofed with mucoid fluid expressed and a sample for HSV DFA was obtained. Based on clinical findings, dermatology diagnosed the infant as having sebaceous hyperplasia; treatment with acyclovir was recommended until the PCR test result was obtained. Pediatric ID evaluated the patient after the initial dermatology

consultation and was unable to evaluate initial vesicles before unroofing. Based on the consultation with ID, the lesions were more consistent with sebaceous lesions than with HSV. In addition, ID noted that maternal HSV IgG would be largely protective against congenital infection. Perinatal HSV is very rare in the first 1 to 2 days after birth and the lack of maternal genital lesions at birth, absence of cutaneous lesions in the infant, as well as the lack of any clinical signs of infection made a diagnosis of HSV less likely. A skin biopsy specimen was taken and sent for pathologic examination but was of insufficient size and thus inconclusive. CSF and blood PCR testing and DFA for HSV were negative and the infant remained well appearing without developing further lesions. The infant was discharged from the hospital on day 4 after birth.

Three weeks after birth, the mother reported that the infant’s oral lesions had fully resolved without recurrence.

Lessons for the Clinician

- A thorough physical examination, including of the oral mucosa, is important in all neonates.
- Vesicular lesions are concerning for herpes simplex virus (HSV) infection of the skin-eye-mouth, but can be consistent with benign dermatologic diagnoses.
- When concerned about HSV, it is important to aggressively treat because of the high mortality rates.

Note: The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the US Army Medical Department, the US Army Office of the Surgeon General, the Department of the Army or the Department of Defense or the US Government.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the etiology and differential diagnosis of bullous skin lesions.

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1

Vomiting and Bradycardia in a Newborn Infant

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PRESENTATION

A male infant is born at 39 weeks and 5 days' gestational age via normal spontaneous vaginal delivery to a 21-year-old gravida 1, para 0 woman with no known medical problems. The pregnancy is uncomplicated and prenatal laboratory results are all unremarkable. Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. Initial newborn examination findings are within normal limits. The infant is born with a birthweight of 3.34 kg, head circumference of 32.3 cm, and length of 52.1 cm, with all measurements plotted to be appropriate for gestational age. The infant is noted to be tolerating breast and bottle feeds well and is voiding and passing stools normally. He is discharged from the newborn nursery 2 days after birth with normal physical examination findings and a weight of 3.3 kg, which is 1.2% below birthweight.

Four days after birth, the infant is brought back to the birth hospital for feeding intolerance and having increased nonbloody, nonbilious vomiting with phlegm after each feeding. In the emergency department (ED), the infant is noted to have lost 12% of his birthweight. He is also found to have self-limiting episodes of bradycardia with heart rates in the 70 beats/min range. Electrocardiography is performed, which shows sinus bradycardia. He receives two 10-mL/kg boluses of normal saline, and the heart rate improves to around 100 beats/min with intermittent dips to around 90 beats/min. The infant's other vital signs are otherwise within normal limits for age. A full sepsis evaluation is initiated in the ED and the infant is started on ampicillin and gentamicin treatment for presumed sepsis. The lumbar puncture is unsuccessful, but blood and urine culture specimens are obtained. Rapid testing for respiratory syncytial virus and influenza A and B has negative results and the chest radiograph is normal. Complete blood cell count reveals a white blood cell count of $8,000/\mu\text{L}$ ($8.8 \times 10^9/\text{L}$), with a normal differential, hemoglobin of 17.6 g/dL (176 g/L), hematocrit of 53.2%, and platelet count of $409 \times 10^3/\mu\text{L}$ ($4.09 \times 10^9/\text{L}$). The basic metabolic panel is significant for hypernatremia, with a sodium level of 151 mEq/L (151 mmol/L). The sample is hemolyzed and the potassium level is not reported. Other values are within normal limits with chloride of 112 mEq/L (112 mmol/L), total bicarbonate of 22 mEq/L (22 mmol/L), glucose of 73 mg/dL (4.05 mmol/L), blood urea nitrogen of 11 mg/dL (3.9 mmol/L), creatinine of 0.55 mg/dL (48.6 $\mu\text{mol/L}$), and calcium of 10.1 mg/dL (2.5 mmol/L).

The infant is transferred to a level III NICU for further evaluation and management. Abdominal radiography is performed on admission to the unit, which shows an overall 'gasless' abdomen and a cystic lucency projecting over the lower mediastinum (Fig 1). He is given nothing by mouth on admission and

AUTHOR DISCLOSURE Drs Cheang, Kaur, Haleem, Borole, and Velazquez have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

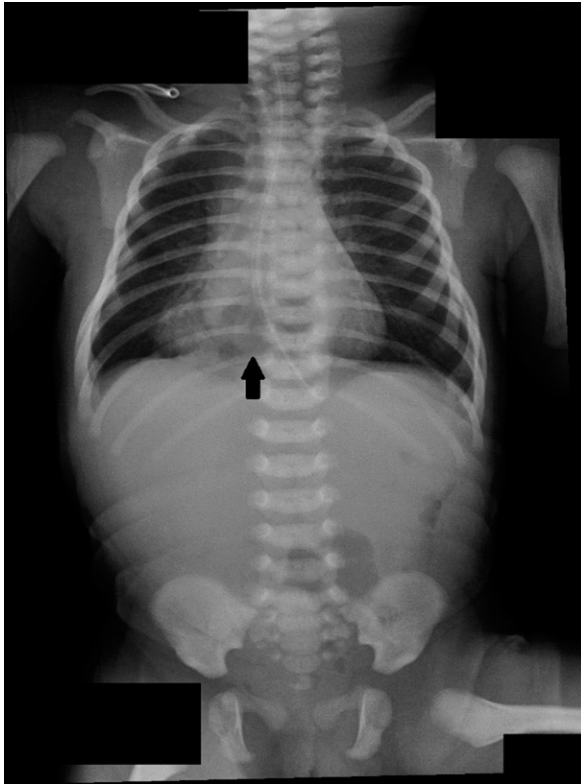


Figure 1. Radiograph depicting a 'gasless' abdomen. The black arrow points to a cystic lucency projecting over the lower mediastinum.

started on intravenous fluids. Pediatric surgery is consulted and computed tomography (CT) of the chest, abdomen, and pelvis is completed, which shows a complex gastric hernia with the gastroesophageal junction above the diaphragm (Fig 2). A subsequent barium esophagography confirms a hiatal hernia or intrathoracic stomach with significant partial obstruction (Fig 3). Echocardiography is also performed, which shows a structurally normal heart with good function but an external impingement on the posterior aspect of the left atrium is noted.

A diagnosis of a hiatal hernia with compression of the heart is made, which is likely the factor contributing to the episodic bradycardia. The infant is taken to the operating room 8 days after birth for open repair of the hiatal hernia with gastrostomy tube placement. A gastrostomy is placed to provide support or hold the stomach to the anterior abdominal wall. Intraoperatively, the infant is found to have a small diaphragmatic defect and a large portion of the proximal stomach in the chest, with only the distal stomach and pylorus in the thoracic cavity. The stomach is reduced and the hiatal defect is repaired with crural approximation.

The infant has no postoperative complications and is able to tolerate ad libitum feeds by mouth before discharge on postoperative day 6. No further episodes of vomiting or

bradycardia are noted and he demonstrates appropriate weight gain. The infant is discharged from the hospital with instructions to the family to follow up with pediatric surgery 2 months later. On outpatient follow-up, he continues to gain weight appropriately, and the gastrostomy was reversed successfully without complications.

DISCUSSION

Congenital hiatal hernias are very rarely seen in the neonatal period and are characterized by a herniation of the abdominal organs, most commonly the stomach, into the thorax from a physiologic opening caused by the laxity of the attachment of the stomach and gastroesophageal junction. Congenital hiatal hernia has to be distinguished from the congenital diaphragmatic hernia, which is a separate entity where there is a pathologic defect in the diaphragm. There are 4 anatomic classifications of hiatal hernias, types I, II, III and IV. Type I or a sliding-type hernia is the most common type, accounting for more than 90% of cases. (1) Type II or a paraesophageal-type hernia, although considered a rarer type, has a higher risk of complications such as incarceration, strangulation, complete gastric herniation with organo-axial volvulus, and a perforation of herniated viscera. (2)(3) Type III is a combination of type I and II, and type IV is characterized by the presence of a structure other than the stomach, such as the omentum, colon, or small bowel within the hernia sac. (1)

Congenital hiatal hernias may present with symptoms such as respiratory distress, vomiting, poor feeding, failure to thrive, poor feeding, or signs such as bradycardia as observed in the current case when the hernia is massive enough to cause cardiac compression. These signs and symptoms have a broad list of differential diagnoses including sepsis, gastroesophageal reflux disease, pneumonia, pneumatocele, pneumothorax, pleural effusion, and congenital diaphragmatic hernia. The diagnosis of hiatal hernias is usually made with a barium swallow esophagography, upper endoscopy, or CT scan showing the herniation of intra-abdominal contents into the thorax. (1)

Although rare, there have been 9 reported cases of congenital hiatal hernia diagnosed antenatally. (4)(5)(6)(7)(8)(9) All of the reported cases were identified during the third trimester of pregnancy. It is postulated that the late onset of findings is because of the fact that the fetus may only be able to develop sufficient pressure to dilate the intrathoracic stomach by the third trimester. Hence, with the development of adequate pressure during swallowing and likely with the effect of reflux of gastric secretions into the esophagus, the dilated esophagus/stomach may be



Figure 2. Computed tomography scan of the chest, abdomen, and pelvis with the white arrow pointing to a gastric hernia with the gastroesophageal junction above the diaphragm.

visualized during third-trimester ultrasonography. (8) This finding has been described as a presence of a cystic mass in the posterior mediastinum, usually located behind the heart juxtaposed to the vertebral body and connecting to the intra-abdominal stomach. (7)

Surgical correction is the treatment of choice, especially in symptomatic paraesophageal hernias with obstructive symptoms. Patients may also be asymptomatic; however, because of the risk of subsequent complications, elective surgical treatment is necessary shortly after diagnosis. (10)



Figure 3. Barium esophagram confirming a hiatal hernia with the black arrows pointing to an intrathoracic stomach with significant partial obstruction.

Lessons for the Clinician

- Although rare, congenital hiatal hernia should be considered in a neonate with gastrointestinal symptoms, such as vomiting, and respiratory distress.
- Early diagnosis and surgical treatment are important to prevent complications and morbidity of hiatal hernia such as aspiration pneumonitis, gastric ulcers, gastric dilation, perforation, gangrene, and ultimately, cardiopulmonary arrest.

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- Know the morphogenesis of the GI tract and factors that lead to congenital malformations.

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